U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
ADVISORY COMMITTEE

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MEETING

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THURSDAY, APRIL 16, 1998

The Committee met in Versailles Rooms I and II, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland 10814, at 8:00 a.m., Paul W. Brown, M.D., Chairman, presiding.

PRESENT:

PAUL W. BROWN, M.D.	Chairman
WILLIAM FREAS, PhD	Executive Secretary
DONALD S. BURKE, M.D.	Member
LINDA A. DETWILER, DVM	Member
LEON FAITEK	Member
BARBARA W. HARRELL, MPA	Member
DAVID G. HOEL, PhD	Member
WILLIAM D. HUESTON, DVM, PhD	Member
LAWRENCE B. SCHONBERGER, M.D.	Member
PETER G. LURIE, M.D.	Temporary Voting Member
DORIS OLANDER, DVM	Temporary Voting Member
ELIZABETH WILLIAMS, PhD	Temporary Voting Member
DON FRANCO, DVM	Industry Liaison
DOUG ANDERSON	Speaker
DAVID ASHER, M.D.	Speaker
RAYMOND BRADLEY, FRCVS, FRCPath	Speaker
BOB BREWER, DVM	Speaker
YUAN-YUAN CHIU, PhD	Speaker
KIKI HELLMAN, M.D.	Speaker
THIERRY SALMONA	Speaker
REINHARD SCHRIEBER	Speaker
WILLIAM STRINGER	Speaker
DAVID TAYLOR, PhD	Speaker
CAROL VINCENT	Speaker

ALSO PRESENT:

SUSAN ALPERT, M.D., PhD
CHARLES GREEN, PhD
JOHN HONSTEAD, DVM
MITCH KILANOWSKI
LARK LAMBERT
PHILIP MERRELL
ROBERT G. ROHWER, PhD
DENNIS WALKER

PUBLIC COMMENT:

LAURIE CLARK
JEAN LOW

I N D E X

INDEX: (continued)

PROCEEDINGS

Time: 8:03 a.m.

DR. FREAS: Good morning. Would you take your seats, please.

I would like to welcome you to this, our second day, of the Transmissible Spongiform Encephalopathies Advisory Committee. Now I would like to go around the table and introduce to you those members of the Advisory Committee who are at the table.

Starting on the audience's right is our industry liaison representative, Dr. Don Franco from the National Renderers Association.

Sitting next to Dr. Franco is Dr. Raymond Roos, Chairman, Department of Neurology, University of Chicago.

Coming around the corner is Dr. Linda Detwiler, Senior Staff Veterinarian, U.S. Department of Agriculture.

Our Chairman, Dr. Paul Brown, Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Strokes.

Next to Dr. Brown is Dr. Donald Burke, Director and Professor, Center for Immunization

Research, Johns Hopkins University.

Around the corner is Ms. Barbara Harrell, our consumer representative, Director, Division of Minority Health. That's for the state of Alabama, Department of Public Health.

Next are our three temporary voting members for today. They are Dr. Peter Grant Lurie, visiting assistant research scientist, University of Michigan; Dr. Doris Olander, research associate, University of Wisconsin; and Dr. Elizabeth Williams, professor, Department of Veterinary Science, University of Wyoming.

The following members could not be with us here today. They are: Dr. Stan Prusiner, Dr. Edmund Tramont, Dr. Katherine O'Rourke, Dr. Dean Cliver, and Dr. David Hoel.

The conflict of interest statement that was read into the public record yesterday remains in effect today, and will remain in effect for the rest of the meeting and, therefore, will not be reread into the record.

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

CHAIRMAN BROWN: Thank you, Bill. It's too bad we have a few extra presentations. I see we've got some late sleepers. We could take a quick

vote. Oh, well.

We have a final presentation from the industry this morning, and then it will be followed by a couple of presentations by government, USDA and FDA. The industry presentation will be by Doug Anderson, titled "Continuing Perspective in Rendering." Mr. Anderson.

MR. ANDERSON: Thank you very much.

This morning I really only want to take the opportunity to summarize a little bit of what you were presented yesterday, to be sure that if there are any questions that those can be cleared up, and again talk about the rendering industry, which is essentially the environmental service provider of essential services to the food processing industry

It's something that we have been doing commercially for more than 160 years, and it's very notable that meat and bone meal has been used in animal feed for more than 75 years in the United States.

You were given descriptions yesterday about edible fat processing, about inedible fat processing, and I think the one thing that you do have to recognize and understand in the United States and that is that, if it's edible, it's edible because of

Federal inspection. That's what makes our food products edible versus inedible in the United States.

It's very possible, probable and practical that products that are made edible are then used edible, but they can also be used inedibly. Once a product in the United States is classified as inedible and unfit for human consumption, it is not allowed back into the human food chain. It can be deemed classified for inedible processing and recycling and reused in the proscribed manners already described.

The production: You've had a sufficient description. As in industry, because of the disease related issues, there have been many initiatives taken in order to protect the American consumer, our cattle feed, our human feed, and entirely across the board.

Traceability is one of the very important things that the use of HACCP programs, the use of ISO programs, any types of quality assurance will require -- do require and are being put into place and have been put into place by our industry. It's something that will further the protection of the food chain as we know it.

Edible products, again, can be produced under Federal inspection by a company that can have any owner. There are inedible captive renderers who

own edible rendering plants. There are meat packers who produce edible meat that have inedible rendering plants.

So it has to be very carefully looked at to make sure that we don't get caught up in a definition as we're looking at where the product comes from, where the product goes to, and whether or not it has been under Federal inspection.

I thank you for your time. I'm available for any questions relative that may have come up to you since the presentations yesterday. Thank you for your time.

CHAIRMAN BROWN: Thank you. Does the committee have any questions for Mr. Anderson? Ray?

DR. ROOS: So -- Yesterday I think we heard Dr. Taylor's results which suggested that a particular processing was optimal from the point of view of decreasing infectivity most significantly, and on the basis of that recommendations were made in UK and, in fact, the whole European Union.

I wondered what the impact would be on the renderers in the United States if such a recommendation was made or a guideline made, and how you yourself would feel about that.

MR. ANDERSON: The industry typically will

follow any guidelines, recommendations and rules that are made by the government. However, we feel that any of those rules and regulations should certainly be scientifically based, and they should certainly relate to diseases that exist within the area and the region that those recommendations are made for.

CHAIRMAN BROWN: The second part of that question, though, was what impact would that have on the rendering industry in terms of changing to that method. Is it going to require the stripping down of every rendering plant in the United States and rebuilding it? Is it a minor modification? Tell us about that.

MR. ANDERSON: It would virtually require the rebuilding of every rendering plant in the United States in order to -- I presume you're referring to the 3bar recommendation.

CHAIRMAN BROWN: Yes. Was that also true in Europe? Did it require rebuilding all of the rendering plants in the UK? And if not, why not?

DR. TAYLOR: I think, generally it's, if not total rebuilding, it required quite a lot of add-on expense. I don't know the precise scale of it.

CHAIRMAN BROWN: Ray, do you have any comments?

DR. BRADLEY: No, but in the UK, of course, we're not feeding any meat and bone meal at all to any food animal species. So the requirement is not in place. We're not actually processing all our material at 133 3bar 20 minutes.

CHAIRMAN BROWN: What are you processing?

DR. BRADLEY: According to the first Commission decision, which eliminated the first two processes which David showed us yesterday in regards to BSE ineffectiveness in decontaminating BSE infectivity. So we're operating satisfactorily in that regard, but not to take out scrapie agent as well.

CHAIRMAN BROWN: All right. Let me recapitulate. What exactly are you rendering or requiring to be rendered, according to David's minimum standard?

DR. BRADLEY: Nothing.

CHAIRMAN BROWN: Nothing?

DR. BRADLEY: Nothing.

CHAIRMAN BROWN: Who is? What's its purpose then?

DR. BRADLEY: Yes. The rest of Europe has to do that.

DR. DETWILER: I asked this yesterday, but

how many really -- We've tried to find out how many countries really have retooled all their plants, and we have yet to have been able to find that out.

DR. BRADLEY: In some countries, of course, long before the Commission decisions were made, either of them, they were already using 133 3bar 20 mins or very, very close to that, which made it a fairly simple process to adapt to the new rule; but -- Pardon?

DR. HUESTON: That's the Germans.

DR. BRADLEY: Yes, and some other countries.

DR. HUESTON: Some of them anyway.

DR. BRADLEY: I think Austria and --

DR. HUESTON: Not all of them.

DR. BRADLEY: Not all of them, no, and there are certainly plants in France, for example, which were not operating to that, and they would have to come to that standard, according to the Commission decision. Whether or not they have done so is a matter for their governments to tell you.

My understanding was, as I mentioned yesterday, that those plants which were operating below the required standard were only being used to render poultry material which, of course, is not

subject to that temperature restriction.

CHAIRMAN BROWN: So the sense of what the European Union is doing is that they are not recommending this minimum rendering temperature and pressure in any country or for any material that is judged to be either minimal or zero risk.

DR. BRADLEY: It's for all mammalian waste.

CHAIRMAN BROWN: I'm sorry?

DR. BRADLEY: All mammalian waste has to be rendered under the Commission decision to this standard, 133 3bar 20 mins. That is the Commission standard for all member states.

CHAIRMAN BROWN: Including the UK?

DR. BRADLEY: If it is to be used as feed for cattle, any species -- any species.

CHAIRMAN BROWN: Or process or go into tallow or gelatin.

DR. BRADLEY: Well, it wouldn't apply to gelatin, because that's a completely different manufacturing process. For tallow, that's not a requirement for tallow. It's only in regard to meat and bone meal.

CHAIRMAN BROWN: Okay. So the recommendation is only in regard to meat and bone

meal.

DR. BRADLEY: No. The Commission decision is very clear. It is ruminant -- Sorry -- mammalian waste that all has to be processed by this procedure before it can be utilized in animal feed as meat and bone meal.

DR. ROOS: So isn't that tallow?

CHAIRMAN BROWN: Waste would include tallow.

MR. ANDERSON: No. The way that it's being done is only for mammalian meat and bone meal, because the Commission decision allows pressurization of the meat and bone meal after it's been rendered. As long as the meat and bone meal has been subjected to the 133 3bar for 20 minutes.

CHAIRMAN BROWN: So the renderers in Europe would render any way they have been rendering, but the meat and bone meal part or greaves of that rendered material would have to be further rendered or subjected to the standards of temperature and pressure?

DR. BRADLEY: Exactly, if it was to be fed back to animals.

CHAIRMAN BROWN: Yes, but if it was to go into a tank, then you wouldn't --

DR. BRADLEY: Yes.

DR. ROOS: But some of the tallow is used in feed.

MR. ANDERSON: And tallow is not subject to the requirement, even in Europe. Tallow is --

DR. ROOS: Didn't you say that anything used in feed --

DR. BRADLEY: I'm sorry?

DR. ROOS: I thought you said anything used in animal feed. So if animal -- If tallow is used in animal feed, wouldn't it be subject to this? No?

MR. ANDERSON: Meat and bone meal.

DR. BRADLEY: It is related to the feeding of meat and bone meal to animals, and in the UK with this idea not to feed this to any food animal species, not even to pigs or to poultry. In the rest of the Community, all countries feed meat and bone meal to pigs and poultry, but such meat and bone meal must be processed by this procedure.

CHAIRMAN BROWN: Okay. So it seems now reasonably clear. You render according to your inner lights, and if the meat and bone meal product from that rendering is going to have any use, then it gets subsequently re-rendered or subjected to the standards

of temperature and pressure that David mentioned to us. If it is not going to be used for animal feed, then it need not be further processed. Is that correct?

Are there any other questions? Yes? Comment from the floor.

DR. MERRELL: It was my understanding yesterday that the tallow had no BSE infectivity in this process at all and, therefore, it's not included.

DR. BRADLEY: We can't hear.

CHAIRMAN BROWN: He said that it was his understanding yesterday that, since tallow is noninfectious, it doesn't need special consideration. Of course, that's exactly what the committee is going to decide.

DR. TAYLOR: Yes, on face value that could be a reasonable interpretation of the data, but in the presentation I'm about to give, I'll explain what the pitfalls in that argument are.

CHAIRMAN BROWN: Exactly. If everybody in the world had already decided that there was zero infectivity in tallow, we wouldn't be considering tallow. Right.

DR. ROOS: So we're going to break down the discussion into tallow and tallow derivatives?

MR. ANDERSON: Correct.

DR. ROOS: Maybe you could just clarify for me how much of tallow is used as a nonderivative form with respect to humans, and for what? I got the feeling some of it goes back to feed perhaps, but perhaps you could clarify that.

MR. ANDERSON: If it comes from the edible fat processing, it can be used in the human as a human food. It's used as a frying shortening. It's used in many foods, baking, etcetera, on the edible fat side. Okay? If it's edible tallow produced under Federal inspection, then that finds its way into a lot of human food.

Edible tallow produced as that specification can also find its way into inedible uses such as derivatives, oleochemicals, animal feed and such. On the inedible side, you have the fact that it goes for animal feeds. It goes for industrial products, cosmetics, etcetera, after further processing. It certainly doesn't go on just as tallow, but that also goes through other processing

CHAIRMAN BROWN: But the great bulk of edible tallow finds its way to human beings. That is virtually all of it. Is that right? Edible tallow.

MR. ANDERSON: I wouldn't say virtually

all, but I would say a large portion of it does find its way to human use, yes, of the edible tallows.

CHAIRMAN BROWN: Yes. Presumably because it's of a higher standard and, I suppose, is worth more per pound than inedible tallow.

MR. ANDERSON: Well, it's strictly based on the quality of the fat, based upon its color and its properties.

CHAIRMAN BROWN: Yes. So it would be sort of a waste to use it as animal feed.

MR. ANDERSON: Correct. It would be a very expensive choice as animal feed, yes.

CHAIRMAN BROWN: Larry?

DR. SCHONBERGER: To follow up a little bit on Raymond's question in terms of exposure of humans to tallow and tallow derivatives, I wondered if my concept that the human -- average human would be exposed to perhaps 10^2 more of a dose of tallow than of tallow derivatives on average. Is that a fair sense?

MR. ANDERSON: More tallow than tallow derivatives?

DR. SCHONBERGER: That if you were --

MR. ANDERSON: No.

DR. SCHONBERGER: That's what I'm trying

to get.

MR. ANDERSON: I would consider it the other way. There would be more opportunity for contact with derivatives than with the tallow, because it's the derivatives that go into the other products that are consumer used products.

DR. SCHONBERGER: By volume?

MR. ANDERSON: Probably by volume as well, yes. The oleochemical industry is a very, very large industry that consumes a lot of inedible tallow.

CHAIRMAN BROWN: I think we'll move on now. Thank you and, if there are further questions, there will be another opportunity in about an hour to ask them.

The next presentation, therefore, is going to be given by David Taylor, who has previously been introduced.

Incidentally, the next three presentations are all focused on the current regulatory policies with respect to tallow and tallow derivatives.

DR. TAYLOR: Thanks very much, Paul.

I've been asked to tell you about and comment on the kind of EU situation with regard to tallow, in which some opinions have been recently offered.

I suspect that there are probably representatives of industry here who have gone over these proposals with a finer tooth comb than I have. So I make any obvious errors, please do advise me here.

The question as to whether tallow is safe has been considered on a number of occasions in the past, and between the years 1994 to 1997, both the WHO, German Federal Health Authority and other respectable bodies have generally said, yes, it is safe. However, last year the EC multidisciplinary scientific committee cast some doubt on this. They basically were saying maybe not, let's look again, and they established a working group to look at the question.

We discussed yesterday some of the evidence which suggests that tallow, if not absolutely 100 percent safe, is certainly very low down on the risk scale. Initially, there was evidence from John Wilesmith's epidemiological study from which he concluded that the geographical variation in the incidence of BSE in the UK was not consistent with the distribution and use of tallow in cattle feed.

We discussed briefly yesterday also data coming from the spiked rendering studies involving BSE

and scrapie where, although we looked at only a limited number of tallow samples, a pair of tallow samples came from the processes which produced the least amount of inactivation as far as meat and bone meal was concerned.

So in the BSE run, we had meat and bone, in this case, affecting 50 percent of the mice that received it, but in none of the animals that received tallow from the same process.

Similarly, in the scrapie run the same process produced meat and bone meal which was infectious for 100 percent of the mice that were injected with it, but in none of the animals that received the tallow.

From these facts you can clear out with the figures of it. In the scrapie spiked run, 12 mice received a total of 6.245 mils of ten percent unfiltered tallow. So from that you say that, as that amount of material had contained 1 ID_{50}, then six mice on average would have been affected, but no mice were affected. Therefore, that volume contained less than 1/6 of an intracerebral ID_{50}, which is equivalent to 0.03 ID_{50} per mil. So that was in ten percent tallow.

Therefore, the neat tallow must have had less than .3 ID_{50} per mil. However, that was an

intracerebral dose. If you want to relate that to oral dose, Richard Kimberlin in the UK has produced a figure of 200,000 representing the difference in efficiency between intracerebral and oral dosing for BSE agent. This is scrapie, and he would admit, it's a fairly ballpark, crude type figure, but it gives you some idea of the scale of the difference.

That would be, therefore, equivalent to $10^{-4.2}$ oral ID_{50} per mil. If you accept the fact that there are no evidence to suggest that these diseases are ever or may be caused by cumulative dosing as opposed to single effective dose, then -- and you assume that the species barrier effect between cattle and mice is the same as for humans and mice, then you can say a human would have to consume almost 16 kilos of infective tallow over a short period to have a 50 percent chance of developing disease, even if there were minuscule levels of infectivity there.

I'm not saying this is a very precise set of data, but they do give you some idea, I think, of the relative risks.

CHAIRMAN BROWN: David, let me interrupt you for just a second. The other way to interpret, if you go back to the first slide, which is a slightly different read on the same data, is that it's true,

one mouse would have to consume 16 kilograms; but let's assume that one infectious unit were, in fact, present at the start, as you've said.

That means at some point, if those 16 kilograms are spread out amongst a million mice, that one of them is going to have a bullseye and die.

DR. TAYLOR: Oh, yes.

CHAIRMAN BROWN: In other words, if there's an infectious unit in tallow and there's nor eduction in that infectivity through processing, that infectious unit is going to find its way to somebody.

DR. TAYLOR: Oh, yes, sure.

CHAIRMAN BROWN: Okay. That's just -- I mean, there's a way to look at this that suggests, forget it, but there's always a way to look at it to suggest let's not forget it, and let's keep talking about it.

DR. TAYLOR: That's why I made the point that I'm not claiming these are very precise calculations, but giving you some ballpark idea.

Before going on to discuss the scientific steering committee opinion in Brussels, it's important to reemphasize things that were said yesterday, and that is that in the recommendations, they refer to risk factors for tallow which relate to the countries

of origin and the nature of the raw materials.

The problem is that the -- in Brussels, while there's not much difficulty in defining a high risk country and a country perhaps of unknown TSE status, they have not yet come out and said what their definition of categories 2 and 3 will be.

The other problem is, as you know, that what will eventually be defined as specified risk material has not yet been defined and will not be for sometime. The only inkling that we have at the moment of the way things are changing is that bovine lung is not likely to be an SRM.

There was a scare that infectivity would get into bovine lung as a consequence of the method of slaughter. It's now believed that this only applies to these very high pressure guns working on compressed air.

It's also considered that bovine ileum which, as Ray showed yesterday in the pathogenesis study, appears to become infected, can be sufficiently and reliably separated from the rest of the gut to be able to declare ileum only as a specified risk material, and the rest of the gut to not be.

Again, a bit of sitting on the fence as far as deciding about sheep tissues are concerned,

because what I read into what has come out is that they are waiting for some sort of risk assessment relating to the real risk of BSE being in sheep, at least in the UK.

They've categorized tallow into these four types: For human or animal consumption or application; for injection; for industrial use, but that's not for tallow derivatives; and category 4 for manufacturing tallow derivatives.

Now the question was asked before I spoke about guaranties and purity of tallow. Despite the data which I've shown which says we have found nothing in tallow, one has to accept that there is some degree of contamination of tallow with protein. Therefore, there must, at least theoretically, be the possibility of infectivity being in there at some sort of level, albeit very low, from time to time.

So one of the plights of the proposals of the SSC is to use purification processes with tallow which will remove protein, and these have been described to some extent yesterday involving either centrigation, filtration through diatomaceous earth, coagulation and then centrigation using phosphoric acid, combinations of the above methods.

The levels to which these should be --

these proteins should be reduced have been declared to be these levels, and that being equivalent to residual nitrogen levels of less than 0.02 percent, and that residual peptides or polypeptides should have a molecular weight of less than 10,000 daltons.

Either publicly or privately, I'd be interested to hear what UK renderers think of the practicalities of these.

Okay. As to the actual recommendations, where the material is for animal or human consumption or application and the raw materials are declared fit for human consumption -- this is by both antemortem and post mortem inspection of the abattoir -- then if the materials are from a high risk area, they're saying that you need to exclude the SRA, process the material by the 133 degrees Centigrade process, if the raw material is not exclusively from discrete and clean lumps of fat tissue, and you also apply a purification process.

This has caused -- this is the opinion. It has caused a bit of debate, because personally I think it's crazy, but you could go into your butcher shop and buy muscle, liver, kidney from animals in this category, and eat them raw in your own home, if you wished; but if you're going to consume tallow from

this animal which has come from anything other than discrete adipose tissue, you will have to autoclave it by this process. That doesn't, to me, hang together.

Category 2: If the raw materials are from lower risk areas, exclude the SRMs and apply a purification process.

CHAIRMAN BROWN: Excuse me, David. On that first point, how would you -- In the UK -- and let us suppose you've got a herd, is it -- are livers and kidneys and so forth and pancreas and thymuses which all would be specified as specified risk materials -- are they in the marketplace?

DR. TAYLOR: No, they're not specified risk materials under anybody's category.

CHAIRMAN BROWN: Spleen is not? Spleen, you don't eat anyway, but sinus.

DR. TAYLOR: Well, spleen is an SBO, yes So is thymus, but --

CHAIRMAN BROWN: I'm sorry?

DR. TAYLOR: Thymus and spleen are SBOs or SRMs.

CHAIRMAN BROWN: Right.

DR. TAYLOR: What I mentioned were tissues that you could go into your butcher shop and buy.

CHAIRMAN BROWN: Liver, for example.

DR. TAYLOR: Liver, pancreas, all legally.

CHAIRMAN BROWN: You could go in and buy a liver in any butcher shop in the United Kingdom now, and you wouldn't know -- well, maybe you would. Would that liver possibly come from a cow in a herd that had had a case of BSE?

DR. TAYLOR: Yeah, technically. Yes. It would be under 30 months.

CHAIRMAN BROWN: It would be under 30 months old?

DR. TAYLOR: Yes. All human consumption material must -- bovine material must be under 30 months at slaughter.

CHAIRMAN BROWN: But, of course, we know that viscera are infected early, if they're infected at all. What's the point of it?

DR. BRADLEY: Only the distal ileum in cattle, as I've showed in the pathogenesis study, not any of these other --

CHAIRMAN BROWN: Yes, so far. Right.

DR. BRADLEY: Well, no, complete, up to 30 months --

CHAIRMAN BROWN: No, no, no. I understand what you're saying. I'm saying, so far you haven't got any infectivity in any other organ, but we know in

the other TSEs that infectivity does occur in viscera, and it occurs early rather than late.

So what I'm saying is in principle, in a heard that had had BSE diagnosed, a cow or a steer from that herd that was clinically healthy would be butchered, and the liver could be --

DR. TAYLOR: Yes.

CHAIRMAN BROWN: Okay.

DR. TAYLOR: But as Ray said, the pathogenesis study is not showing anything in all these peripheral tissues. Okay.

If the raw materials are from a lower risk area, exclude SRMs and apply a purification process. if they're from a BSE free or negligible risk area, apply a purification process.

What to say about countries with an unknown TSE status is try to carry out a risk assessment and, if you can't do that meaningfully, regard it as high risk. This suggests to me that, because the country is described as having an unknown TSE status make sit unlikely to be able to carry out a meaningful risk assessment, and you'll be forced into describing it as high risk.

The second category is tallow from -- for animal or human consumption application where the raw

materials are unfit for human consumption. Again, the SSC are sitting on the fence, because they are in a bit of a dilemma, because they know that within that category, at least within the EU, the raw materials can and will include fallen stock, condemned carcasses, sick animals, zoo animals and even laboratory animals.

So they have still to define the minimum processing conditions, and the interim recommendation is that anything that comes within that category at the moment should be fed only to animals, even in BSE-free countries, because of the risk of sporadic case of BSE.

One of the categories was tallow for injection. This is not to be confused with tallow derivatives -- tallow for injection, and there are, at least within the EU, currently no known examples of this.

For industrial use but not for tallow derivatives, if the materials to be used are fit for human consumption, the only restriction is that you apply a purification process. That policy changes as the raw materials are unfit for human consumption.

I think the ethos here is that people using large volumes of tallow based product in the

industrial setting may be unaware of what they're handling, and so you do have to protect them in some fashion. So the recommendation is a process by the 133 pressure system, and apply a purification process.

Further, they say that if the end use is unknown -- in other words, you can't guaranty that people are sloshing around in this stuff -- that the conditions relating to the different geographical sources as applied to human consumption material derived from raw materials fit for human consumption should apply.

For the production of tallow derivatives, if the materials are fit for human consumption, there appear to be no restrictions; but if you're using any other type of raw material -- it's relatively vague, but the way I read it is that you use procedures that are inactivating for BSE agents during the manufacture of the tallow derivatives.

I think Dr. Green yesterday gave us a rather convincing and eloquent demonstration of the fact that the procedures that are used for, as far as I could gather, all of the tallow derivatives are -- would be considered to be fairly reliably inactivating for TSE agents.

Now we're not talking about procedures

that have actually been validated, but -- with regard to that characteristic, but over the years these procedures have been looked at by a number of committees who have all concluded that they cannot conceive of TSE agents surviving these splitting type procedures.

So I think we could probably regard these as -- generally regard it as safe type procedures.

That's my understanding of the SSE opinion, but if anybody has spotted any major blunders, I'd be happy to hear from them. Thank you.

CHAIRMAN BROWN: Thank you, David.

The European solution reminds me a little bit of Schedule D of the IRS form. Lord, I hope that we don't get into that. That's a very complicated set of recommendations.

Are there any questions for David? Linda

DR. DETWILER: Dr. Taylor, what prompted the SSC -- or the MDSE, I'm sorry, to say maybe not Was there something specific or was it just a limited data, because it's a difference -- right? -- from earlier rulings?

DR. TAYLOR: You mean what prompted them to look at tallow again?

DR. DETWILER: Right. To say maybe not.

DR. TAYLOR: Well, as you know, the whole way in which the EC operates in terms of concerns about BSE and TSE has had a shake-up over the last 18 months, two years. It's my view that the previous system was actually very good, but that's not the way the EC actually considered it.

So new brooms sweep clean. I think with the concern, to be fair, over human health, the people in whose lots the responsibility now lay felt we have to relook at all of the existing data.

I don't -- I think maybe I went too far when I said that the MDSC said tallow is maybe not safe, but to be more realistic, I think they said, well, perhaps we should look at this through fresh sets of eyes and convene a working group.

Is that your understanding, Ray?

DR. BRADLEY: Yes.

CHAIRMAN BROWN: Has anyone spiked tallow with a conventional virus to show that you can actually demonstrate infectivity in something with a consistency of tallow, one.

Two, how did you get the tallow into suspension for inoculation? I would have thought -- I know you made a one to ten. How did that work?

DR. TAYLOR: It actually emulsified not

too badly in a grinding tube. It just suddenly formed what to be a colloidal suspension.

CHAIRMAN BROWN: I don't know if --

DR. TAYLOR: The reason we used ten percent is that we couldn't get the big tallow through the needle into the --

CHAIRMAN BROWN: Yes, of course. You can't inject a candle into a mouse's brain, but it's a curious point about -- You know, I don't know if anybody -- I'm unaware of anybody trying to detect infectivity in butter, for example. I just don't know how you do it.

If there are no precedents for this material being able to have infectivity detected, I don't know what to think.

Other questions? Yes?

MR. ANDERSON: Dr. Taylor, in the one description of the peptides or the polypeptides, there was a pick of a molecular weight of less than 10,000 daltons. Is there some scientific basis for that, or what was that pick?

DR. TAYLOR: I guess it was probably a mix, a compromise of what was perceived to be achievable and based on the fact that the infectious core of the PrP protein is somewhere around 27,000

daltons.

CHAIRMAN BROWN: As far as I know -- and, Bob, you may be able to correct me -- there is no experiment on the books in which infectivity has been detected in any filtrate going through a 10kd filter. Is that correct?

DR. ROHWER: No. There are several publications which have claimed to find infectivity on the other side of alterfilters and nanofilters. However, none of those experiments have been controlled very well, and there's certainly a whole 'nother body of -- well, there's not a lot of data, but there are several other experiments which indicate that infectivity is not past a 30 nanometer track etched type filter, which has a very precise pour size definition.

CHAIRMAN BROWN: So there are sizing experiments on which that number is based. I guess there's no exact equivalence between sizing nanometers and kilodaltons. So you choose one or the other. Probably the securest data is based, as Bob said, on nanometer sizing rather than molecular weight sizing, but in general the size has been -- It's pretty small infectious particle, and that is the kind of cutoff that has been historically used as a good filtration

system for removing infectivity.

DR. TAYLOR: Can I just comment, Paul. I mean, I don't think this implies that you will or you will need to use molecular cutoff filters. They're saying that you can achieve that, even by filtering through reasonably deep beds of diatomaceous earth. That's my understanding of the situation.

CHAIRMAN BROWN: Thank you, David. I think we'll move on now to the final two presentations before the committee is required to make some decisions.

They will be, first -- Excuse me, three presentations. They will -- No, two. They will be, first, by Dr. Bob Brewer of the USDA and FDA,m and Dr. Chiu is also listed in both presentations. I'm not quite -- Okay. Doctors Brewer and Chiu, in some order.

DR. BREWER: Well, I'll just try to amplify a bit on what we said yesterday and, hopefully, answer a few of your questions. FSIS is also a low tech/low budget operation. So we'll resort to overheads, too.

Our conversation today is basically around tallow, of course, and it was kind of interesting to look at tallow. Would you put the next overhead on

there, please?

I looked at Dorland. That seemed to be a good place to start with this crowd, and it was a very concise definition. Tallow is described as suet. The next definition, please.

Yo look at suet in Dorland, and it says it's the fat from the abdominal cavity of a ruminant in the preparation of cerates, ointments and as an emollient in pharmacy use. It is the external fat of the abdomen of a sheep. That probably is a reflection of what Dorland is involved with, and I don't think we can produce any -- as far as I can determine, we are not producing any edible tallow from sheep in the United States.

Next slide, please. This is Webster's International Unabridged dictionary. It's rather old, but it's, I thought, a pretty good definition: Animal fat, suet, rendered fat of cattle, sheep, composed of glycerides, etcetera, used to manufacture soap, glycerol, margarines, and lubricants.

The last, please. This is an interesting dictionary that USDA provides to us. It's not a very reliable dictionary. You should look further most of the time, but they're talking about tallow as being a product from the bodies of cattle, sheep or horses,

and again certainly there's no edible tallow from horses being produced in the United States.

Okay. There's a little interesting commercial fact about tallow. It's long been a factor in the United States or in the land of the United States. The California Spanish missions were set up by Spain for three purposes. One was to control the land for Spain, of course. One was to save souls, and one was to be a commercially viable operation. I'm not sure in what order that was to be done.

Their are two main exports back to Spain were tallow and cattle hide. So we've had a long history of producing tallow in this country.

Next slide, please. FSIS's involvement with tallow comes under Title 9 of the Code of Federal Regulations, and these are the various parts, and it's very scanty. There are four different parts listed there, but probably it would take you about three minutes to read all four parts of it. Take you longer to find them than it would be to read them.

Next slide, please. I think this is a crucial point for this crowd. All raw material for edible tallow has to come from an officially USDA inspected plant. It has to be from inspected and passed animals. It has to be from a recent production

lot.

In other words, you can't accumulate this tallow, have it around in storage for a couple of months and then decide to produce an edible tallow from it. It has to be kept in good condition, stored at 50 degrees or less before it's processed, and unless it's moved directly from the kill floor or the rendering units.

Now from a practical standpoint, most of the tallow in the United States comes from a very few plants. I think Dr. Franco mentioned yesterday that we don't have a lot of plants producing edible tallow. We have -- USDA inspects approximately 1100 slaughter plants. Fifty of those 100 plants produce 85 percent of the production.

We've got -- These plants -- Some of these cattle plants are killing as much as 7200 head a day. A number of the swine plants are killing 15,000 swine a day, and they produce -- One plant kills 22,000 swine a day, and we only have five sheep plants that kill 90 percent of the lambs in the United States.

So we don't have a lot of the plants that actually wind up producing this edible tallow. Certainly, no more than 50 plants are producing edible tallow products, and these are all USDA inspected

plants.

Any of these plants that bone away from a USDA inspected plant or fabrication plant are not, for the most part, as far as I can determine, producing any edible tallow. That all goes to the inedible tallow.

In the USDA inspected plants, these animals are, as I said yesterday and I'll repeat -- they are inspected at movement, and they're inspected at rest in the corrals. If they pass that inspection, they go into the plant. They're slaughtered. They're inspected again by another inspector, and in the big plants these are lay inspectors. That is a fact of life.

Then if they pass that inspection, they proceed on down the line. They go through the final stages of processing before they go into the coolers, many of these plants are now using steam or hot water pasteurization. They're rinsed in a steam cabinet or they're exposed to live steam in a steam cabinet, or to 160+ degree water and a 20-second rinse, and then many of them go from that rinse into an acidic acid rinse, two percent acidic acid, and rinsed again, and then they get a final just potable water rise and go into the chillers.

Then there in the chillers, they're held there for 24 hours up to 36 hours where they're chilled; and while they're in these chillers, they are spray misted for 60 seconds every hour with a 20 parts per million water spray. That helps reduce the temperature down.

So up until a couple of years ago, most plants were holding these animals 24 hours before they started breaking them down and fabricating them. Also at that time, some of them were removing the fat at the end of the line, the so called hot fat removal.

Well, that did not produce the results they thought it would. The idea of that originally was to reduce the energy requirement for cooling the carcasses, and it didn't make any difference.

So they've gone back to chilling them now, and then they remove that fat 24-36 hours after they're killed and before they're fabricated, and that is the fat and the fat that's derived from the fabricating processes that winds up in most of the edible product in the United States, and that's virtually all that winds up in the edible tallow.

Once it goes from off that kill floor and goes into the rendering process, it is put into rail cars or trucks and moved to some other establishment,

and at that time when it's put into the cars or the trucks, it's sealed by USDA, and that's the end of USDA's involvement in it.

So where it goes to -- and after that, it falls under other jurisdictions.

I would like to mention one thing that kind of bothers me a little bit. I've practiced for 32 years and I have a lot of family involved in the livestock business, and we keep hearing the fact that there might be one animal per million with BSE each year in the United States, and we're not finding that.

Well, we have about 110 million cattle. So that would translate to 100 head of cattle or so, and I strongly believe, and I think most veterinarians in this room would agree with me, that if there's 100 animals out there with BSE in the United States, somebody sure as hell is going to find them, because he would have his career made. It would be a real feather in his cap.

I think, at the same time, any people that are routinely losing animals that are producers, like my brother died three years ago. At the time he was milking about 2,000 cows; and if he was losing a cow or two a year, he would know about that, if it was BSE. He would certainly take it to somebody and find

out what was happening.

So I really don't think that it's a viable option to talk about missing all these BSE animals out there.

Then finally, I want to make a few comments about the downer cow or the non-ambulatory cow issue. That is a bit of a can of worms, to be frank about it. There are a lot of different sides to it. There's a humane issue, certainly; but again, an awful lot of the so called downer cows or non-ambulatory cattle are animals that are injured by one way or another.

I was in a plant two weeks ago in California that ordinarily gets about 20 of these cows a day. Most of the time, they're Holsteins that have slipped on cement and, if a Holstein tries to get up two or three times, is not successful, they no longer try.

So different lengths of time they're allowed to remain on the farm, because these people's hope springs eternal, but most of them do wind up at a slaughter facility to be slaughtered or attempt to be slaughtered, salvaged for something. But at that time, because of the rains and the conditions that had been existing in California and is attributed to El

Nino, they were getting 90 downers a day in there.

A lot of these cows are being injured in the process of the conditions that existed in the corral. So an awful lot of the downer cattle in this country are due to injuries. So I think that that's something that, again, I personally don't perceive the downer cow as being a great source of problems to this.

I've kind of rushed through this, but I do want to reiterate that any edible tallow, I think, is adequately inspected at this point, and I think that the veterinarians are not primarily involved in inspecting for edible tallow production, but in part of their oversight in the boning rooms and in the slaughter floors, they are very careful to ensure that contaminated product does not get into the edible product line.

The final comment will be made about spinal cords. Again, from a practical standpoint spinal cords are not going into these advanced meat recovery systems for a couple of reasons.

Most of these spinal cords are removed either at the end of slaughter line or certainly very early in the hot boxes, because the spinal cords had a tendency to fall out on the floor; and when the

people washing the floors the next morning in the coolers wash these down the drain, then you have to call Rotor Rooter to dig them out.

So they're very careful to take them out, and they were selling them for a while; but that market is pretty well collapsed, too. I was talking to a packer the other day, and he said they're so cheap that it does not pay them to salvage those. They were sending quite a lot of them to Japan and to Central America.

So if I can answer any questions, I'll be around here all day. I'll certainly try to do that. Thank you.

CHAIRMAN BROWN: Questions for Dr. Brewer? Yes?

DR. OLANDER: How does the inspector evaluate the neurologic status of a non-ambulatory animal?

DR. BREWER: Well, those animals are inspected by veterinarians, and it's somewhat subjective. I'm not going to pull your leg, but I think most of these people have been there a long time, and it's -- they can't do a CAT scan or anything that esoteric, but I think that most of them -- I don't think that's a particularly difficult thing to

do, to determine the central nervous status of an animal.

Now if you want to back up a little bit and we'll get Linda involved in this, I think that some of these downer cows come in, and they should not be brought to slaughter plants. I think they should be examined before they leave the farm or the ranch or the dairy and be examined by an accredited veterinarian. A lot of those animals wouldn't arrive there, because they come in comatose. Well, then they're condemned anyway.

DR. OLANDER: What is the role of state inspection -- state inspected plants in the tallow flow?

DR. BREWER: In tallow flow? Well, for the most part, state plants are very small entities. Even USDA -- We have plants that kill ten head a year, believe it or not, and we provide Federal inspection to them. It's just not a very good use of resources, but we do that.

Some of the small state plants are down in that kind of number, too, and there really aren't any large state plants, but state plants have an inspection system that's supposed to be the equivalent to, but as far as I can determine, none of the state

plants are producing product that goes into edible tallow. That all goes into inedible product, as far as I can determine.

CHAIRMAN BROWN: Thank you very much. Dr. Chiu.

DR. CHIU: Good morning. I would like to thank the committee for coming and spending time in helping us to make a very important decision. I would also like to thank all the people. You provide a very valuable information, and I also would like to thank all the FDA staff for helping us to prepare this meeting.

I'm going to give you a review of FDA policy and the requirement on tallow and the tallow derivatives. I'm going to go over the related use, the use of tallow and tallow derivatives regulated by FDA, and also the current product quality standards, FDA inspections, and also the susceptibility of countries for sourcing.

Next slide. The regulatory status of tallow and tallow derivatives in FDA relate is based on its end use. Yesterday we have heard edible tallow and the hydrogenated tallow can be used as food, also can be used as food ingredients or food additives.

We also know inedible tallows from a

renderer can be used in animal feeds. Both edible and the inedible tallow and the tallow derivatives are used as a component of many cosmetic preparations. FDA does regulate cosmetics for human use, but not for animal use.

We also learned, most likely, edible tallow derivatives are the ones used for human and animal drugs. Although we do not have official data in-house on dietary supplements, however, because dietary supplements are prepared either like food or like a drug, therefore, the use of tallow and tallow derivatives for drugs and foods probably applicable to dietary supplements.

Next. We also heard the limited tallow derivatives such as glycerin being used in medical devices and in biologics. How those uses are really used of these tallow/tallow derivatives as a component of the final product. However, tallow derivatives such as the surfactants or glycerins are also used in a different way; that is, to be used as a reagent in the manufacturing of bulk drugs or medical devices.

Next slide. Next I'll give you a little bit of marketing data we have in FDA. The data presented in this slide is a 1992 data for tallows consumed/sold in this country.

You see there are 693,000 metric tons of edible tallows sold as food or used in food. Out of this, 194,000 metric tons are sold for -- as frying fat in places such as McDonald's. So it translate into like seven grams per day per person.

Regarding edible tallows in 1992, 1,400,000 metric tons was sold. More than 50 percent of that is used in animal feed. We also have data showing 20,000 metric tons of edible tallows are imported. It constitutes less than three percent of the market by volume.

You have this slide in your handout -- next one. The next slide you have in your handout. It may not be very visible from the screen.

This slide gives examples of tallow derivatives or tallow used as food or in food or in cosmetics. In FDA there is a voluntary registration program for cosmetics. There are over 16,000 cosmetic products marketed in this country. However, much less of that number has been registered at FDA.

On the lefthand side are the substances used in the cosmetics, and on the righthand side is the number of products contain those substances. Because a product may contain multiple substances on this list, therefore, the sum of the number of

properties is less than the number of products.

Next slide. This slide is also in your handout. It is used to illustrate the wide use of tallow derivatives in pharmaceuticals. On the lefthand side, the left column, we put the causes of oleochemicals used in pharmaceuticals.

They are fatty acids, fatty acid salts, fatty alcohols, fatty acid esters, tallow glycerides; and the polyglycerides, triglycerides, diglycerides, and the monoglycerides.

After that will be fatty nitriles and the amines and the glycerins. The substances under each type of chemicals are just used as examples. The common ones are listed. There are many others not listed in this table.

The middle column gives you the information on the functions of those substances used. They serve either as emulsifier agents, solubilizing agent, lubricant, dispersant, and have warming agent, surfactant, antimicrobial preservatives, waxing agent, solvent perentals, sweetening agent.

All those components are substances that are in the final formulated dosage form. So they are a component of the drugs. Under the dosage forms and the route of administration of these products cover

almost every possible dosage form and every means of administration.

CHAIRMAN BROWN: Dr. Chiu, excuse me. Is toothpaste included somewhere?

DR. CHIU: Yes. Toothpaste is considered oral. I think it's an MPC.

CHAIRMAN BROWN: Well, that's okay.

DR. CHIU: I don't think --

CHAIRMAN BROWN: I just wondered if toothpaste were one of the -- considered a cosmetic in that sense.

DR. CHIU: No. Toothpaste can be considered either cosmetic or as drugs. If toothpaste has prevention of a disease such as tartar prevention, then it becomes a drug. So some of the toothpastes are regulated as drugs, but this list does not include toothpaste. So probably either our data is not complete or because they did not use one of those components.

CHAIRMAN BROWN: And are tallow derivatives used in toothpaste?

DR. CHIU: I have to go back to check, because my list does not include toothpaste. If toothpaste is used, we would consider it sort of like a oral drug.

Next one. So because the tallow and tallow derivatives are widely used in FDA regulated products, so they have different regulatory status. As you heard from Dr. Brewer, once the tallow leaves the rendering plant, then it's under the jurisdiction of FDA.

So under the food regulations, then tallow to be used in food, then it will be covered by the food good manufacturing practices, and also where it needs to meet the food labeling requirements.

There is no need to submit application for premarketing approval. The only substances which require FDA premarketing approval for tallow or tallow derivatives in area of food is for food additives.

Many of the tallow derivatives are considered generally recognized as safe. So those substances would not require premarketing approval. They would need -- Many of them meet food chemical Codex standards, and for tallows we heard yesterday, the standards -- quality standards and specifications are established by the American Fat and Oil Associations.

The components used in cosmetics actually are very loosely regulated by FDA. It does not require premarketing approval, and that is the color

additives.

Then for drugs, the tallow derivatives -- Tallow is not used in drugs, but tallow derivatives are. Because they do not serve a pharmacological function, they do not have pharmacological activities. So we consider them an inactive ingredient, and collectively we call them excipients.

Many of the tallow derivatives are GRAS substances, and they meet either Pharmacopoeial or National Formulary standards, and they also will need to meet other standards established -- is established in our Code of Federal Registry.

Next one. Because the tallow derivatives are either food or most likely for the ingredients -- most likely, they are GRAS and they are also excipients meeting USP or NF standards. So ordinary submitting documentation on its manufacturing process and the quality controls to the agency usually are not required.

FDA rarely inspects the manufacturing establishments of drug excipients. What we -- in the pharmaceutical area, what FA inspects are the pharmaceutical manufacture of the active bulk drug and the dosage forms. We make the pharmaceutical manufacturer responsible for the quality of the

excipients used, as approved by the agency in the application.

Next one. The next two slides will give you an example of what kind of quality standards we're talking about. The first example is fatty acids as food additives, which is listed in 21 CFR 172.860.

It stated -- The regulation stated fatty acids must be derived from edible source. It contains not more than two percent of unsaponifiable matter by using a method specified in Association of Official Analytical Chemists.

Then it also must be free of chick-edema factors. You can either use a bioassay or use a GEC methods specified in AOAC.

The next example is USP grade of glycerin. The Pharmacopoeia stated that glycerin must contain 95 percent to 101 percent of the glycerin molecules. Then you provide passive specification for chemical identity, physical property, and purity, in addition to assay.

So from these examples, you see none of the quality standards would address the safety related to the BSE.

Next one. So in order to assure that bovine derived product will be safe in the context of

BSE and not contaminated by BSE agent, the agency has taken a series of actions. The agency -- As you heard yesterday from Dr. Bailey, the agency has issued a series of letters and published notice in Federal Register, and also issued new guide -- new regulations on feed ban and also issued a guidance document on gelatin.

Next one. The essence of those recommendations issued which are applicable to tallow and the tallow derivatives is illustrated here. The first one is the bovine source material: Not to use materials that have come from cattle born, raised or slaughtered in BSE countries, according to USDA.

The reason for this recommendation is we felt, in order to have safe product, you must have clean materials, to start with. Therefore, sourcing from the BSE-free countries we are assured the final product quality.

The second recommendation is about records keeping. The agency recommends to identify bovine derived materials used in FDA regulated products, and document the country of origin of the live animal source; maintain traceable records; and maintain records at the site of manufacture; and make them be available for FDA inspections.

Then later on we did -- In 1994 we did provide exemption of the requirement for BSE-free sourcing to gelatin, milk and milk derived products, and last year we revoked partially the exemption applicable to gelatin. However, there is no exemption up to today for tallow and the tallow derivatives.

Yesterday we were asked to provide you with a table to delineate the status of different substances in relation to its use. So this table was made last night.

On the lefthand side, the left column, we have the substances, gelatin, edible tallow, inedible tallow and the tallow derivatives. The first row specifies all the different types of product. The first one is injectable, ophthalmic, implantable products, followed by oral products. That includes food, oral drugs, dietary supplement, nutrition supplement.

The third columns are drugs administered the other routes. The fourth column, cosmetics, then followed by animal feeds.

The "yes" and "no" in the database stand for the acceptability of BSE countries for sourcing. So if it's stated no, it means BSE countries are not permitted. If it says yes, it means it is permitted

with or without restriction.

Under gelatin other drug products, I put down yes. However, based on our database, a very few products other than oral products contain gelatin. So, therefore, our gelatin guidelines did not specifically mention products administrated by other means than oral or injectable.

Then in parenthesis, when I say not used, it means we have not identified that substance used in that product. I was advised this morning under animal feed, edible tallow was specified not used may not be complete true. It depends on the price. So when the price is good, the edible tallow may be used in animal feeds.

I'll stop here and answer any question you have, then go on to next one, the questions.

CHAIRMAN BROWN: Yes. Thank you, Dr. Chiu. Any questions for Dr. Chiu before we move on? Are you now going to read us the questions we are to address?

DR. CHIU: And I'm going to give a little background, then have questions -- then go on questions. Yes?

DR. SCHONBERGER: You said in your talk that the average person -- or the tallow consumption

in the United States came out to about seven grams a day per person. I had asked that -- I'm trying to get the sense of exposure to these various products to an average person in the U.S. and compare tallow with tallow derivatives. I'm more interested in the comparison.

I was under the impression before this that we were more exposed to tallow, because I can see that. I go to a hamburger joint or something and get french fries, and I'm getting exposed to tallow, and I can, you know, go to a bakery and I'm exposed to tallow, get some soup or something like that.

The derivatives seem to become -- I get exposed to in very small amounts like if I take a pill or something like that.

DR. CHIU: Exactly.

DR. SCHONBERGER: But I was just told that I'm more exposed to the derivatives than I am to the tallow. So --

DR. CHIU: I think you are more exposed to the different kinds of derivatives, but in terms of quantity, if we are thinking about going through pills or dietary supplements, then the amount is very little. If magnesium stearate, typically the use is just a few milligrams per tablet, and actually most of

the filler we use in pills is lactose.

DR. SCHONBERGER: In your own -- So you're giving me another -- In your own view, my exposure to tallow versus the tallow derivatives by volume, the way you're thinking of it, is ten times greater, double or 100 times greater? What -- In your own mind, what kind of difference are you thinking in terms of in my exposure to tallow versus tallow derivatives? Just trying to --

DR. CHIU: Well, that's very difficult to estimate. It depends, first of all, whether you take pills routinely, whether you use cosmetics routinely, and also you use shampoos and other cleaning agents, and also we use soap every day.

So I think when you talk about all those combined, you may be exposed significantly, but if you want me to give a figure of five or three times, it's very difficult.

CHAIRMAN BROWN: You and I have less need for shampoos than most.

DR. SCHONBERGER: That's right. Exactly. I also don't wear that much cosmetics, but unfortunately, I go and eat a lot of food. Too much.

DR. HUESTON: If I understand your calculation correctly -- I didn't do the math, but

seven grams is actually the -- That's the total use of edible tallow divided by the number of people in the United States.

DR. CHIU: Right.

DR. HUESTON: And the vast majority of that is actually not consumed. When you go into the -- at least the last time I went to a fast food place, they didn't give me a little container of the grease to drink after I had my -- So the majority of that grease simply gets recycled or in some way -- It isn't actually totally consumed.

DR. CHIU: No. It's not all consumed. It's sold, though, and it's sold to fry french fries. You eat french fries. You will not eat the grease. Most of the grease probably is just throughout. DR. HUESTON: So it's probably safer to say that it's seven grams of edible tallow that's sold as opposed to consumed.

DR. SCHONBERGER: Will, what's your assessment of the exposure? You know what I'm trying to -- Do you have your own sense that we're more exposed to derivatives?

DR. HUESTON: Well, I was interested by the -- That's why I asked this question, because I was fascinated. My gut feeling is the same as yours, that

our exposure to tallow is greater than our exposure to tallow derivatives in terms of a volume.

I'm interested -- Doug, throw it back at him.

MR. ANDERSON: If you're talking about how much do you eat -- I mean, if you talk about the tallow that you consume as being part of the steak or part of the hamburger that you eat, that's an entirely different story, because that's not tallow produced as tallow. That's a human food that's being, you know, worked out in the fast food restaurant.

When you talk about going to a fast food restaurant and eating fries, unless you don't remember what Mr. Sackalov said USA Today a few years ago, most every fast food restaurant in the United States doesn't use edible tallow to fry their french fries. They use vegetable oils.

So, you know, I think that when you talk about an exposure situation from eating french fries, you're probably not going to come into contact with any of the edible tallows anyway. If you talk about fat consumption as part of the foods that you eat, that's an entirely different topic than, I think, what we're talking about here today.

Here we're talking about tallow that's

been produced in an edible fashion from Federal inspected plants. And that's where I'm coming from.

CHAIRMAN BROWN: Excuse me just a second. Dr. Brewer, did you have a comment? We're starting to lose a little --

DR. BREWER: I wanted to make a comment that would go along with what Doug was saying. One of the companies told me last week that in 1990 they had ten plants producing edible tallow, and as a result of what's happened with the french fry market going to vegetable shortenings, they now have one plant producing edible tallow, and nine of those plants are producing tallow, what they call technical tallow, that goes into soaps, and it's enough -- all these bird feeders.

They're selling huge tons of that, these little square blocks of bird seed. So they probably make more money doing that, but also it's going into some dog foods, too, but they've gone from ten plants to one plant.

CHAIRMAN BROWN: Dr. Chiu, is this -- In what way will this presentation depart from the previous one? What are we now --

DR. CHIU: Oh, it will be a little different, just two slides, and then will be

questions.

Before we discuss the questions, I would like to mention the factors which has impact on the safety of tallow and tallow derivatives. The first factors we'd like you to consider is source materials, the sourcing country and its BSE status.

The status could be negative. That means no BSE is reported, and that country also has food surveillance program meeting the OIE requirements.

Then the next category would be, although no BSE is reported, but if the country does not have surveillance program, is not looking for BSE cases, then it's BSE status unknown.

Then you have BSE positive countries, have been divided into high prevalence or high risk, low prevalence, low risk.

The second factor related to the bovine source material would be the slaughtering house procedures. As Dr. Taylor mentioned earlier, for BSE countries, whether you will consider the specified risk material be removed for BSE free countries such as the United States.

The U.S. government's policy is we do not believe SRM removal as proposed by you is applicable here.

Next one. The second part of the factors will be manufacturing process and the controls. The first small category will be in the rendering process which produce edible grade and the inedible grade tallows, and we also heard that there are many different means to making edible grade tallows, the batch process, continuous process.

Then the manufacturing process for tallow derivatives: We have heard many different ways, and we know for further derivatized the derivatives, then it will go through even downstream processing.

The last factors will be the end use. For tallow it can be used in food and cosmetics, and that we do not know the status of dietary supplement. For tallow derivatives, I separate the end use into four classes: Cosmetics, topicals, and the transdermals, which are delivered through skin.

One topical put on open wound will be very similar to an injectable product. The second category will be through oral route, food, nutrition and dietary supplement and oral drugs.

Third category: Drug administered via nasal, otic, rectal and the vaginal routes. Most of them go through mucous membrane.

The fourth one, the injectable:

Ophthalmic, inhalation through bronchia or lungs, and the implantable products.

These four categories may not be proper. You may want to consider to combine them into just two, injectable and the others, or you want to divide them into more categories.

Next one. So the charge for the committee is to assess the safety of both imported and domestic tallow and the tallow derivatives, with regard to the risk posed by TSEs, specifically TSEs.

The first question: Does the available scientific information justify a change in the current FDA guidelines that bovine source material for the rendering of tallow should not come from BSE countries as designated by USDA?

If you recommend a change, then should FDA consider changes to the guidelines for tallow used in food and cosmetics? Should FDA change the criteria of sourcing countries? Should we make recommendations on the slaughtering procedure, and what are they? If the sourcing country can be from BSE countries, then should an SRM be removed? Should we make recommendations on the rendering process, and what are they? Should -- May inedible tallow be used in cosmetics?

Question 3: The next question would be on tallow derivatives. We separate them into -- We made a separation, because we think you may have different answers for the tallow from tallow derivatives. So the question will be just repeated.

Number 3: Does the available scientific information justify a change in the current FDA guidelines that bovine source material for manufacturing of tallow derivatives should not come from BSE country, as designated by USDA?

The last question: If yes, should FDA consider changes to the guidelines for tallow derivatives used in food, cosmetics, nutritional and dietary supplements, and a drug administered via various routes?

Even though we did not put down biologics and medical devices because few derivatives are used there, the recommendations to human drugs will be applicable to medical devices and the biologics.

The specific questions will be on sourcing countries and slaughtering procedures and tallow quality controls, on manufacturing process and process controls for various tallow derivatives.

Thank you.

CHAIRMAN BROWN: Thank you, Dr. Chiu.

I am, frankly, intimidated by what we're being asked to do today. This is the point when the Chairman really ought to be able to bring into focus and guide the committee's discussion and deliberation, and I don't know if I can do that.

I think the first thing to be clear about is that the third slide from the last which Dr. Chiu showed is not something that I think, frankly, this committee should be involved in, and that is a consideration of whether the entire process of producing tallow sourced in this country ought to be in some way changed or altered.

My understanding of what this committee's charge was in the written material was that we are not going to try and dictate what the rendering committee does with respect to tallow when the tallow is sourced from this country.

If we're expected to do that, we're not going to have time to do anything else this afternoon. So I would ask the committee if they agree with that. It is not, in my judgment, our business to evaluate rendering and tallow processing in this country from U.S. sources.

It wasn't a question. That's the point. It was a slide before the questions in which we were

said to be evaluating not only international but domestic procedures, and I don't want to evaluate domestic procedures, if I don't have to do it.

If that were the case, we should never have been asked to deal with gelatin, dura mater and tallow in the same meeting.

DR. HUESTON: Paul, can I -- So I'm trying to figure out. I, too, thought we were restricting our discussion on tallow and tallow derivatives --

CHAIRMAN BROWN: Through BSE countries.

DR. HUESTON: -- sourced from animals outside of the United States.

CHAIRMAN BROWN: Exactly.

DR. HUESTON: Is your concern that question number 2 leaves off all the preamble and says should FDA consider changes in guidelines for tallow used in food and cosmetics, and that could be --

CHAIRMAN BROWN: Well, I don't know. I'm looking at the sheet with the four questions that we were all handed out sometime ago, and those were the questions that Dr. Chiu read. The four questions are the questions that I would be prepared to consider.

Of course, we could punt and say no to questions 1 and 3, and immediately proceed to other subjects; but we are not going to do that.

DR. CHIU: May I make a clarification?

CHAIRMAN BROWN: Yes, please do.

DR. CHIU: If you restricted your answer to BSE-free countries, then you don't have to address the slaughter house procedure. We would very much like you to consider if you expand to BSE countries or BSE status unknown countries, then whether we should implement something on the process and on the slaughtering house procedures.

So when you said we restrict it to U.S. products, then we do not need that you make any changes. We are not expecting you to make any recommendation to the U.S. practice of rendering.

CHAIRMAN BROWN: That's fine. In other words, we're going to consider the questions as written, and we're not going to worry about the slide which preceded your question slide, which asked us to consider domestic as well as international procedures.

Maybe I'm reading more into that than everybody else is, but when I saw the word domestic, it raised a red flag. So let us then consider the questions as they were presented to us as questions. Ray?

DR. ROOS: One question related to this first question, which has to do with the guidelines

that bovine source material for the rendering of tallow should not come from BSE countries.

Maybe I need some more education about this, but kind of remembering back, I got the feeling that all of the source material for tallow has to be -- - in the United States has to be collected locally. Isn't that what we kind of spoke about at one point? We didn't?

CHAIRMAN BROWN: No. I believe that several presenters indicated that a very small proportion of raw material tallow was imported, mostly from Canada.

DR. ROOS: From Canada?

CHAIRMAN BROWN: Yes. Well, this is --

DR. ROOS: I'm wondering whether this is a totally academic question that we're going to spend 20 minutes on which has no implication as far as practice.

CHAIRMAN BROWN: Linda.

DR. DETWILER: I think it might be academic, because USDA regulations would prohibit from BSE countries plus from high risk raw materials that would come in. I mean, they would only allow in certain processed things. So --

CHAIRMAN BROWN: Like what?

DR. DETWILER: Well, as far as tallow derivatives. Our regulations would not preclude tallow derivatives from there.

DR. ROOS: We're just talking about bovine source material for the rendering of tallow.

DR. DETWILER: Right, and our regs would prohibit that, would block them.

DR. ROOS: So should we just move on to question 3, the dura?

CHAIRMAN BROWN: No. I think the -- Let me follow that, since we're agreed that we are going to address these questions, 1, 2, 3, and 4, as the questions to be considered for the tallow stage of today's discussions.

Does the committee agree that the wording of both questions 1 and 3, from BSE countries, will be understood in our deliberations to include BSE-positive countries and BSE unknown status countries? Right. That's a clarification. Now --

DR. HUESTON: Excuse me. Can I add to your clarification?

CHAIRMAN BROWN: Yes.

DR. HUESTON: It looks to me that -- and I know people spent, no doubt, hundreds of hours framing these questions, but there's every opportunity

for confusion as to whether the first question means is the concern over the entry of bovine source materials into the United States, which is a moot point because that's already prohibited, or whether its entry into the United States or used in the United States of tallow which originated from bovine source materials. That's the --

CHAIRMAN BROWN: Yes. This is what Linda, I think, was addressing. Raw materials, source materials, the USDA prevents from coming into the U.S. for any use that relates to humans. So -- or animals.

So I guess we are talking, therefore, about the importation of tallow and/or its derivatives.

Now anybody on the committee has the right to ask anybody in the audience on specific points of information. I'm sure everybody who has presented or most people are still here. I would like one additional or -- not additional, but to be reminded of what proportion of tallow used, sold or processed in derivatives is imported. What proportion of the total U.S. production of tallow or the total U.S. use of tallow is imported? Imported. That's all we're concerned about.

MR. KILANOWSKI: Raw tallow that comes

into this country is about -- I think it was 29,000 metric tons per year coming in from --

CHAIRMAN BROWN: Right. Mostly Canada, yes.

MR. KILANOWSKI: And I would say the bulk of that is coming into and being used for fatty acids.

CHAIRMAN BROWN: Right, but that's the volume or amount of tallow being imported.

MR. KILANOWSKI: Right.

CHAIRMAN BROWN: What proportion of the total tallow use or production in this country does that represent? Was it like 100 percent?

MR. KILANOWSKI: It was like half of one percent, something like that, yes.

CHAIRMAN BROWN: Half of one percent? All right. So, basically, we're talking about a half of one percent of the tallow production or use in this country that is coming under the consideration of this committee.

DR. CHIU: May I make a clarification?

CHAIRMAN BROWN: Yes.

DR. CHIU: We also -- For example, we also import cosmetics. Cosmetics imported may contain tallow which may be sourced from BSE country or BSE free countries. So we need to also consider end

product.

CHAIRMAN BROWN: Okay. So raw tallow and anything down the line that contains tallow that is imported. I presume that's a much more important import than the tallow. Yes, Leon?

MR. FAITEK: That's one of the points I wanted to make. It's not a coincidence that we're not importing tallow. We're using very little imported tallow from BSE countries. It's prohibited. That's why those import numbers are so low.

CHAIRMAN BROWN: Well, Linda was saying that tallow per se is not prohibited. It's the raw materials that are prohibited.

DR. DETWILER: Right.

MR. FAITEK: My understanding was that tallow itself was also prohibited.

DR. DETWILER: No.

CHAIRMAN BROWN: No. That's one of the things we're considering.

DR. DETWILER: Right. Tallow -- Under USDA tallow is one of the products that is exempted, tallow and tallow derivatives, and that would be in accordance with WHO recommendations in accordance with the Office of International Epizootic recommendations.

MR. KILANOWSKI: Let me just say one more

thing. The reason that we don't have a lot of tallow coming into this country is not so much because it's prohibited. It's just that we've got an overabundance of tallow here, and it's being exported every year.

CHAIRMAN BROWN: Yes, sure.

MR. KILANOWSKI: We've got 30 percent that's being exported every year. I mean, it's kind of silly to have imports coming into this country.

CHAIRMAN BROWN: Oh, that's one of the points that was evident from your presentation, which is why I asked why we're importing anything at all.

MR. FAITEK: But is it also prohibited from importation?

CHAIRMAN BROWN: What, tallow?

MR. FAITEK: Yes.

CHAIRMAN BROWN: No. Not now. That's why we're here.

DR. ROOS: So I guess we're breaking up this question into two parts, I think, at this point. One is raw tallow, which sounds like, if you exclude Canada, we're talking about something that, I think, is kind of academic.

CHAIRMAN BROWN: Right.

DR. ROOS: And the second part of the question, which sounds so vast that I'm a bit

overwhelmed, which as I understand it has to do with every cosmetic, every food product coming in the United States that has tallow in it.

CHAIRMAN BROWN: From a BSE or --

DR. ROOS: Right. Again, I just don't know how to deal with that issue. I mean, if we decide it's a bad idea that a product has had tallow from a BSE country and is in use today for a variety of products, which sounds to me like perhaps even a reasonable statement -- you know, what's the implication of our comment that this -- I mean, is there any possibility of policing this, providing documentation?

CHAIRMAN BROWN: Well, let's get to that after we decide if it's necessary.

DR. ROOS: Well, no. Feasibility -- Unless I misunderstand --

DR. CHIU: Let me remind the committee, the current FDA policy is that if a cosmetic -- imported cosmetic, if contains tallow, that tallow must come from the bovine source of a BSE-free country. So that's already the current policy.

So the question is whether you feel tallow is -- because the process is safe enough, then we can go beyond BSE free countries.

CHAIRMAN BROWN: The comment by Kiki yesterday is relevant here. The most likely thing that the committee could do would be in the direction of relaxation. All right? Or not relaxation.

At the moment, all products that contain tallow or a tallow derivative that are sourced in either BSE+ or BSE status unknown countries are prohibited from being imported. That is the current FDA position, and we're being asked --

DR. HUESTON: So it's guidance, not --

CHAIRMAN BROWN: Well, all right, guidance. I'm not an administrator. I always lose track of guidance and regulation and law and so forth, but this is guidance. Right? We'll use the word guidance. Recommendations? Is there any better word than guidance? This is what the FDA guidance or recommendation is. Okay.

DR. HUESTON: As it relates to FDA regulated products.

CHAIRMAN BROWN: Okay. So we don't prevent the importation. We recommend the prevention of the importation.

DR. SCHONBERGER: And do we also recommend the prevention of importation of tallow from such countries?

DR. HUESTON: No. I think we need to clarify. We're talking about for use in FDA regulated products. We're not talking about banning importation. That's not the purview of the FDA. What we're talking about is the incorporation of tallow or tallow derivatives from these source materials into FDA regulated products, devices, etcetera. Did I understand that correctly?

We need to narrow our discussion a little bit. We're talking about a narrower area, I think.

DR. HELLMAN: Yes. Kiki Hellman. Will, that's exactly right, and the word is recommendation. That is what we've used all along. That may later translate into guidance, but right now it's recommendation, and Will has it exactly correct.

So the committee should decide whether there should be relaxation or a lifting of that recommendation for tallow and tallow derivatives.

DR. BURKE: Although we've gotten a listing of products that may contain tallow, I don't have any idea of what the total volume is or where these are coming from. We've talked about sources for the source material. We've talked about sources of the tallow itself, but we have not talked about the sources of who makes the cosmetics and who -- where

are the interests that say that, if this is lifted, what are the implications of this? I have no idea of what the kinetics here in terms of dollars or grams or people or anything else.

CHAIRMAN BROWN: Does anybody in the audience or the spectators have advice on this? Yes?

DR. GREEN: Well, the question, as far as the derivatives --

DR. BURKE: It's not the derivatives I'm asking right now. I'm asking just for tallow itself that goes into products.

DR. GREEN: All right.

DR. BURKE: We're going to address the derivatives, which is a separate one.

CHAIRMAN BROWN: Well, we've been told that tallow per se imported represents essentially a trivial --

DR. BURKE: But that's tallow. That's not processed tallow that is in a cosmetic already.

CHAIRMAN BROWN: That's right. So your question is what is the implication of a recommendation that products in which tallow would be used coming from BSE+ countries.

DR. BURKE: How much manufacturing is made in France? I don't have any idea.

CHAIRMAN BROWN: Yes. Right. Or more appropriately, the UK. Anybody in the FDA have a notion about that?

DR. HONSTEAD: I think the committee needs to orient its decisions based towards the scientific aspects of this thing. Part of FDA's job is to then take your scientific opinion and information and evaluation and merge that with the economics and the enforcement side of it.

So I would limit your debates here to the scientific issues.

CHAIRMAN BROWN: I think that's an excellent point, and it's a point that sometimes we on the committee forget. That's a key word in the question and always has been -- scientific. Barbara?

MS. HARRELL: Are we generally going on -- or is there anything else we're going on besides Dr. David Taylor's study as far as the scientific evidence or information? Is that all we have to go on?

CHAIRMAN BROWN: With respect to tallow, I think that is correct. I'm unaware of --

DR. HUESTON: Epidemiologic.

CHAIRMAN BROWN: I beg your pardon?

DR. HUESTON: And the epidemiologic.

CHAIRMAN BROWN: Yes, sure. There was the

phenomenon of a lack of association between the occurrence of BSE and --

MS. HARRELL: You mean the risk assessment? Which one?

DR. LURIE: I understood it -- Perhaps this was discussed, you know, in a previous version of this committee, but there's an ecological study which looks at the use of where tallow is fed to animals and the relationship between that.

CHAIRMAN BROWN: That's right.

DR. LURIE: And I have to say for myself that, without having seen the study, the design of it, there's little to convince me of the safety of tallow. It seems to me that simply by its ecological design, it adds, you know, very little to what we know. But in any case, that's not -- That's different than the risk assessment.

CHAIRMAN BROWN: The evidence, such as it is, as you say, ecological or epidemiological, was simply a failure of association of the occurrence of BSE and the distribution of tallow. That was one little clue.

DR. LURIE: Yes.

CHAIRMAN BROWN: The other little clue is Dr. Taylor's double study on tallow, both with respect

to BSE and, David, with respect to scrapie as a spike? Yes. In both of those studies which David provided a certain number of qualifications for in terms of conclusions, that is the total laboratory evidence on the absence of infectivity in tallow.

Did you have a comment?

MR. LAMBERT: Yes. Lark Lambert, Office of Cosmetics and Colors. In response to Dr. Burke's question, in our voluntary registration program these are the products that were -- that contain tallow, and you can see there's a very few on the righthand side. The number -- The 01C, that's a product category which is also other baby products, which in this case was shampoo. There was only two products.

These are out of -- Again, the companies voluntarily send in their products to be registered with the FDA. Most of them don't send it in, but if -- There are approximately 16,000 registered products.

For just tallow, not tallow derivatives, these are the product categories that they are under. You can see, most of them fall under bath soaps and detergents and, you know, shampoos are only two. So there's only a small number, really.

DR. BURKE: Thank you. That is helpful, and I do apologize for overextending into the economic

sphere, but I think it is useful to have information on products, routes, dosage and grams. I think those are all part of legitimate scientific components of any decision, and that is useful. Thank you.

CHAIRMAN BROWN: And I think the committee is -- Yes?

DR. OLANDER: One last question. What is the procedure or methods for verifying that we are receiving products that are derived from edible tallow as opposed to inedible tallow from overseas countries?

CHAIRMAN BROWN: Anybody wish to answer that question? Any of the speakers?

DR. HUESTON: Don't they have to have USDA inspection to show that at least meet the USDA? I was looking at Bob.

CHAIRMAN BROWN: Microphone, please.

DR. BREWER: They would have to have an export certificate accompanying this signed by an official in the country that it was being exported from, the United States. Then that certificate would be examined when it came into the United States, of course, by the USDA authority, either an APHIS or an FSIS authority, and you would have to be satisfied that what they have stated on the certificate was accurate and that the product was accurately

described.

DR. HUESTON: Wouldn't edible tallow, since it's coming from essentially animals that are passed -- They would have to meet the same requirements and have to have a USDA inspector there to have equivalency.

DR. BREWER: They would have to have a ante mortem and post mortem inspection, be handled in a separate facility from the inedible. In other words, you couldn't process edible tallow in the morning and inedible in the afternoon and that type of thing. Have to be a facility dedicated just to producing edible product.

Now as far as I know, nothing comes except from Canada in the way of an edible tallow product, and I suspect that's mostly from a couple of plants that are owned by U.S. interests. So that's probably the reason for that.

DR. HUESTON: Are you aware of anything from Europe, Linda?

MR. ANDERSON: One other comment. Even on the slide that was put up there about the products that they register as having tallow as part of the ingredient, if you go back, I'm sure you're going to find that a lot of those are really derivatives, not

raw tallow that are going into those products.

So, I mean, there's a very, very small amount of edible tallow or tallow used in those products in its native form. It would be in a derivative or further processed form.

CHAIRMAN BROWN: Again, to come back to the question 1, as it's worded, we're excused, I think, from concentrating on raw materials, because that's the way the question is worded. Guidelines that bovine source materials for the rendering of tallow should not come from BSE countries.

Answering that question takes care of everything downstream. Now if we decide that there should be some relaxation of this, then we have to get into the downstream side of things, and that's why the slides that you have seen presented by the FDA have broken the use down into things like injectables and orals and cosmetics.

If we get into saying yes to question 1 -- that is, scientific information does justify a change -- then we are going to get into areas downstream, which is overall use products and so forth.

As I say, one of the things you have to sort of ask yourself is if -- you have to assume that this is designed to prevent an infectious unit of BSE

from entering the U.S. as tallow or tallow derivative, and you have to assume that this is designed with that in mind.

Let us suppose that a cow from a herd in the United Kingdom is slaughtered and the tallow is pooled with other cattle tallow, and that's imported for a use or another, an injectable, an oral, a cosmetic. Is that something that you feel would be -- would carry such a low risk that it would not be a problem and, therefore, we would change the FDA restrictions; or do you feel that that does pose "an unacceptable risk" or an unnecessary risk, in which case we leave the FDA current policy intact?

DR. ROOS: Well, I mean, the data that we have, as I see it, demonstrates no infectivity of tallow, although the data is a little bit limited. It seems like there is a very small amount of protein present in this tallow, which also makes one a little bit confident that one doesn't have the infectious agent.

Generally, one is dealing here with a species/species barrier, if one is talking about these tallow products, and I'm just talking about raw tallow for human use; and lastly, we have some processing which involves heat and alkali treatment.

I guess I would ask you, Paul or anyone else, how you felt about the processing of this raw tallow with respect to the heat and the treatment used and how much confidence we should have with respect to that.

If there are issues still remaining with respect to the infectivity and the heat and the alkali treatment, and one is dealing with a BSE country in which BSE is clearly present, I wonder whether one should at this point in time maintain regulations with respect at least to these tallow products, which sound like they're a very small amount of material coming in, at any rate, although I would raise questions as to how many products one is really dealing with and whether, in fact, all these -- crude tallow might also be tallow derivatives.

It's going to get very complicated restricting one and not the other. At any rate, I just wanted to know whether you could put the heat and the alkali treatment in perspective here. No alkali treatment, just heat treatment.

If you remember back to these crude --

CHAIRMAN BROWN: Yes. Well, the tallow --

DR. SCHONBERGER: Can I expand on that, the question, and maybe focus for a moment on Fred

Bader's model. He used 10^{-8} for arbitrary reduction for the tallow derivative. The question would be what would be the comparable figure that you would use for tallow for the effect of the production on the reduction of titer? Would you use something more like 10^{-3}? Is that a better estimate if we were to just consider tallow, given what Ray is asking?

CHAIRMAN BROWN: David produced evidence that the rendering process per se used in most of Europe, with the exception of the autoclave type rendering process -- and tallow is a product of the rendering process -- that all of the other procedures had negligible infectivity reduction.

Says nothing about the infectivity at the start. All we're talking now is about a process. The process of rendering is not an effective inactivant of these agents, and one of the products of the rendering process is tallow, which leads me to just summarize the improbabilities of infectivity.

Number one, a BSE cow that is clinically healthy is a possibility of occurring, but it's unusual. All right? I mean, at the present moment, even in the UK presumably, you have cattle that will come down with BSE that are presently healthy. So the UK is a little special. The other countries are much

less at risk than that.

So the probability of including an cow incubating BSE in the rendering process is a small one. It exists in a BSE country, but that's the first improbability.

The second improbability is --

DR. SCHONBERGER: Well, again, for putting numbers on it, I think in Bader's model it was like it changed to 1 to 10,000 or something.

CHAIRMAN BROWN: I think you would be making a mistake to play those mathematical games at this point. I just don't think there's enough solid evidence to make that a worthwhile route to follow.

DR. SCHONBERGER: I was just trying to go through this exercise in part with Bader's model to see if I was still going to be in the insignificant risk category. If you're telling me that that 10^{-8} has to be thrown out because -- totally -- then he ended up with a 10^{-15}, which was a negligible risk.

If I'm going to add an eightfold increase to that, I'm already starting to get into the significant risk.

CHAIRMAN BROWN: I wouldn't argue from Dr. Bader's conclusion. I think the conclusions he drew were valid conclusions with the assumptions that he

used, but he -- I mean, to get all those assumptions, Dr. Bader would have to come back up here and give us a 15 minute lecture on the assumptions for that particular number.

All I'm saying is that, number one, the improbability of having a BSE infected cow in the rendering process. It would occur, and that's why the BSE countries are called BSE countries, but that's one improbability.

The second improbability is the infectivity, the presence of infectivity in the tissues that are being rendered.

The third improbability is the survival of those infected units after processing. There's a little bit, according to David's analysis -- there's a slight reduction from that process, but short of the process of pressure/heat combination, the reduction is really quite small.

So those are the improbabilities, and those are what we would have to consider and weigh if we say that the FDA can relax a little bit. We have to understand that this is the kind of evaluation we're going to have to get into if we say the FDA can relax on tallow or raw product sources of tallow and tallow products, not tallow derivatives. That's not

this question. This is tallow.

DR. SCHONBERGER: Well, it sounds as if we're dealing with an extremely low risk, but one that may be above what Bader had described as the insignificant level at 10^{10} or something in that area. That's where I'm sort of leaning, and I'm just throwing that out for others to maybe comment and say that we haven't heard anything today to put us into the absolutely insignificant risk category for tallow, and that, therefore, we should change the policy.

That's where I'm leaning right now.

CHAIRMAN BROWN: Well, I certainly agree that the scientific evidence bearing on the question is very limited. Such as it is, it inspires confidence, but it's very limited. Is that fair, David? Wake up.

DR. TAYLOR: Are you asking for comments?

CHAIRMAN BROWN: Yes. The evidence with respect to lack of infectivity in tallow is very, very limited in scope. Such as it is, it inspires confidence.

DR. TAYLOR: Yes, I would agree with that. I would also say that the figures that I've played around with early on which we discussed somewhat, although you can argue with the detail of them, they

do give some idea of the scale of safety that could be associated with tallow.

CHAIRMAN BROWN: It's, in a sense, ironic that the FDA has got us considering, of all the kinds of things that I could imagine coming from BSE infected cattle, a couple of items that are so low down the list of dangerous sources. I mean, it's not like we're dealing with the importation of thymus for baby food. It's really quite a different question.

I don't think we should lose sight of that.

DR. SCHONBERGER: Well, going back to what Bader was asking us to consider was the other side of the equation, is what do we gain by a decision to change? You know, what's the problem that we create by not changing the recommendation and, given what we heard --

CHAIRMAN BROWN: What problem do we create?

DR. SCHONBERGER: You know, when we talked about blood safety and we talk about withdrawing, we had the problem of are we creating a shortage?

CHAIRMAN BROWN: That's the FDA's problem. That is specifically not our problem.

DR. SCHONBERGER: I know.

CHAIRMAN BROWN: Nor should we be considering it.

DR. SCHONBERGER: Well, I thought Bader was trying to tell us to evaluate the -- that there is no zero risk and that this is a risk/benefit type of decision.

CHAIRMAN BROWN: Right. But the FDA was telling us forget the benefits.

DR. SCHONBERGER: I don't -- They were telling us --

CHAIRMAN BROWN: They're going to decide about the benefits. It's their decision to decide risk/benefit analyses. It's our decision to make an estimate of risk.

DR. SCHONBERGER: All right. Well, then I'll just state it so that --

CHAIRMAN BROWN: Is that fair? Is that correct? I mean, would you say that that's what we should be doing? I mean, it's your job to decide about risk/benefit.

DR. HONSTEAD: That's true, Dr. Brown, and it's specific in the question, and it has scientific in it.

DR. CHIU: I think the committee shouldn't -- the benefits to human health, not the benefit

economically, because that's our problem.

DR. SCHONBERGER: Okay. Well, I'll talk in terms of human health then. So the committee -- or the FDA can take that into consideration when they're on their own. I really think we're probably dealing with a non-problem or a problem that's very low, approaching that insignificant level; but I can't be sure from what I heard today that it really is in the insignificant category.

Then I look at the other side and say what's the impetus for me to change these recommendations. What is the problem that exists, if I don't say change it, and I don't see a problem there. So I say why should we do it? That's sort of where I'm at, and I'm opening that up, if people want to go after that.

DR. LURIE: I think that the notion of restricting ourselves to the scientific is on its face attractive, but in practice not really reasonable. I think Don sort of hinted at this.

Part of the scientific question has to do with the degree of exposure of people to the likely or not very likely infectious materials, and that is, in and of itself, related to, you know, the amount of imported material and so forth and so on.

I see it the way you're seeing it, which is that, in effect, the risk of continuing the current FDA policy has not been identified by any speaker that I've heard at this meeting. I have not heard anybody say that there are particularly important products that will somehow not come here. I have not heard that there are any particular medication that will somehow be denied to American consumers as a result of continuing the ban. I have not heard that the existing ban has created that kind of problem.

All of the evidence seems to suggest that the required tallow is available in abundance and that the existing policy has caused no problem. Agreeably, the risks may be small, but it doesn't seem things are broke. So I'm not sure why we need to fix it.

CHAIRMAN BROWN: Comments? Do you want to vote? We're talking again about question number one, tallow as opposed to tallow derivatives. This is just with respect to tallow, and the question is -- and I come back to the word scientific.

I really do think we can limit it to scientific, and I don't think it necessarily boils down to the question of what risks are we taking by not changing it. I think we have maybe more responsibility than that.

I think we have to look at what we heard today and decide whether or not BSE sourced tallow -- excuse me, BSE sourced tallow -- BSE country sourced tallow poses any significant risk to this country and decide whether or not, if it does, then we leave the FDA regulations as they are, intact. If we think that that risk for whatever product -- and we can identify products. We can say, well, cosmetics don't seem to me to be a particular risk, but injectables are.

We have the ability to say to the FDA, yes, continue your restrictions on anything that has this source for injectables or for cosmetics, but relax a little bit on something else.

So it's not a blanket thing. It's not all or nothing. We can decide to recommend to the FDA that they relax on certain things. It's not an umbrella. It's not 100 percent. We have the ability to specify materials which we feel really don't pose a risk and, if so, then there's no logical reason to continue acting as though they do. Paul?

DR. HUESTON: Paul, can I ask just -- I appreciate very much the framework you're setting. Can I try to take that one step further.

If one looks at it at least from my perspective, trying to categorize or evaluate the

risks, certainly, one would say that inedible tallow from inedible rendering has more high risk input material than material going into edible rendering. Follow me?

CHAIRMAN BROWN: Yes.

DR. HUESTON: Because edible rendering is using materials that would be passed for human consumption. So we get back to the analogy that, in fact, you could eat -- you can buy in the store and eat everything that goes into edible rendering. Correct?

CHAIRMAN BROWN: Yes. Absolutely.

DR. HUESTON: Now for -- Part number two then, if we talk about BSE countries, and I think the real countries we're talking about here are really European countries -- So most of those is -- just another side question. Do brain and spinal cord -- do the SRMs currently enter the pool of raw materials for developing edible rendering?

DR. TAYLOR: Not in the UK and not in some other countries, but not in all European member states.

DR. HUESTON: Okay, because in some European member states one can actually still consume brain and spinal cord, if you so desire.

DR. TAYLOR: Exactly.

DR. HUESTON: We know that the processing -- So I think we have a differentiation here between -- In the United States, in fact, we also can eat brain and spinal cord, if we so desire. Right? So we have a differentiation between those things -- the tallow from edible rendering which would normally come into our diet anyway and the tallow from inedible rendering, which includes a whole lot of other things.

It includes most of the high risk animals and a larger proportion of the high risk materials. I'm just trying to help give a framework to it, because I think that comes back then to the uses and to this very nice chart that we have of clarifying where might the tallow enter our -- enter the opportunity to expose.

So as Dr. Lurie is saying, where might be the exposure, and what would be the type of products or the origin of the tallow used in those types of products for which United States citizens might get exposure?

CHAIRMAN BROWN: Why don't we vote on a first approximation, which is do you think that the current FDA blanket restrictions or recommendations to avoid BSE or BSE unknown status countries should

continue to apply; or can we make here today at least some revisions which will open that umbrella and put a few holes in it. Leon?

MR. FAITEK: You clarified it.

CHAIRMAN BROWN: Okay. I'd like to vote on that, and then if we decide that there are certain things which should be relaxed, then that's the next topic of discussion, to decide what those things are.

MR. FAITEK: You're asking us to vote on--

CHAIRMAN BROWN: On question 1.

MR. FAITEK: -- question 1 plus or --

CHAIRMAN BROWN: Just question 1, period. Okay?

DR. FREAS: Dr. Brown, could I just clarify for the audience and for the record that there are currently 11 voting members at the table. Our industry representative and the two guests that have been invited to the table are nonvoting at this time.

CHAIRMAN BROWN: And the members of the committee may choose to not vote, vote with a short statement, vote with a Larry Schonberger type statement, vote yes, vote no, or abstain. Don?

DR. FRANCO: Abstain.

CHAIRMAN BROWN: Larry?

DR. SCHONBERGER: I'll abstain.

CHAIRMAN BROWN: So we have two plus-minuses. Oh, I'm sorry. Don, your vote doesn't count.

DR. SCHONBERGER: Let me pass for a second.

CHAIRMAN BROWN: You mean you want to come back to it after the committee makes its decision? Put it on the line, Larry.

DR. SCHONBERGER: All right, I'll put it on the line.

DR. LURIE: Larry, just a moment. Just let me clarify. A no vote means no change. Is that correct? Let's be clear on that.

CHAIRMAN BROWN: No, exactly. I think that's a good point. We don't want to vote opposite to what we think we do. Right?

DR. LURIE: I think that would be better, yes.

CHAIRMAN BROWN: The FDA has a habit of using double negatives in our questions. Does the available scientific information justify a change in the current FDA guidelines that bovine source materials for the rendering of tallow should not come from BSE or BSE unknown status countries?

In other words, a yes vote is a vote for

the possibility of change. A no vote leaves the current FDA policy intact. Larry?

DR. SCHONBERGER: Okay. Part of my hesitation was that I wasn't -- All the possibilities hadn't suddenly gone before my mind, and there might well be something that I would say, oh, well, that risk is so low, yeah, we could change it; but as a general -- Since I don't have that in my mind right now, I'm going to vote no.

I want to know that, if somebody brings up something that I'm not thinking about that says that there's a use or a certain product that really the exposure is negligible, then I'm right at the border line on that there being any risk at all here.

So I'm going to say no. Just leave it alone.

CHAIRMAN BROWN: So you believe that the scientific evidence does not constitute reason for a change in the current policy?

DR. SCHONBERGER: No change.

CHAIRMAN BROWN: No change. Okay. You understand that a no vote closes the discussion, therefore. So you --

DR. SCHONBERGER: That's why I made my comments.

CHAIRMAN BROWN: You won't hear anything, huh? Leon?

MR. FAITEK: I vote no for the following reasons. One is that I don't see that any change that we could make in the context of this discussion would make the products that use tallow any safer than they are now. Probably quite to the contrary.

I wouldn't try to put a number to that increased risk factor, but I think that there is an increased risk factor there.

Number two, unlike dura mater where if you have a contaminated sample, one person may get sick, which is not to minimize that -- one person getting sick is bad -- but if you're using a pooled product and, although again the possibilities are small of anything untoward happening, the consequences could be large.

Third of all, and this is an area where the statement before says we probably shouldn't be getting into, I would think that the industry would want this added safety for their benefit. God forbid that there's a BSE cow found in this state, and we wind up with a mass of regulations that we heard explained today from the European community.

I think that any change in this regard

would be, I dare to say, which is counter to my heritage -- My view is conservative in this regard -- would be unwise and certainly at the very least premature.

CHAIRMAN BROWN: Ray?

DR. ROOS: I'll vote no. I think there is clearly a very low risk for reasons that people have noted regarding tallow, no obvious infectivity in the studies that we have, small amounts of protein, heat steps in the processing, species to species barrier, etcetera. Still, the negative studies don't rule out the possibility of infectivity and risk here.

We have presently guidelines from the FDA, and I haven't heard sufficient evidence to change the present guidelines, at least from my perspective.

An issue is whether one should deal with this umbrella guideline or whether one should break things away into different categories. At the moment I'm just concerned about dealing with all of those different little pieces, and I'm worried that it's going to be a bit of a regulatory nightmare and a lot of details that, as you described, Paul, look a little bit like an IRS form with different schedules.

So at this point in time, I think I'd like to deal with it as an umbrella with that umbrella, no.

CHAIRMAN BROWN: Bill?

DR. HUESTON: I vote yes. I believe that having this umbrella and this absolute approach to say absolutely no really in the long run is disadvantageous. The reasons are this: One, I think it ignores the science. It ignores the fact that we have opportunities to reduce the risk and to manage the risk that may be present.

I think, secondly, it essentially labels countries for having identified BSE and may further preclude or minimize or damage the encouragement that we're making globally for countries to report the occurrence of disease, and this may in fact encourage countries to pursue policies of hiding disease, an that we are more likely to get high risk materials into the United States as a result of a blanket policy than we would be by having a reasonable -- what I would consider a rational approach which says -- which lays out here are the risks, here are the benefits or the approaches that we can use in processing to minimize or to inactivate the agent, here are the uses which represent very low exposure to individuals.

I think, by that strategy of looking at sourcing, processing and use, one could come up with a very scientifically sound policy that would allow

countries to see a way in which they might be able to market their extremely low risk material in an appropriate manner and might further our, I believe, common and shared goal of global public health.

CHAIRMAN BROWN: Thank you. Linda.

DR. DETWILER: I vote yes also for the same reasons Will did. Approaching this from a scientific base is something that appears to have low -- you know, negligible, if any, risk to begin with, and then taking precautions.

I look at it just like I wouldn't want the government coming and telling me I can't drive an automobile because there's a risk of getting in an accident versus they can tell me I must wear a seatbelt or not drive with alcohol impairment.

CHAIRMAN BROWN: I vote yes, simply because I think the level of infectivity likely to occur in tallow is close to zero, and that being the case, I think that oral products and cosmetics could be easily and safely excluded from this restriction.

Donald?

DR. BURKE: I vote no. I'm not impressed that the risk is zero, and I see little benefit in changing the current policy.

CHAIRMAN BROWN: Barbara?

DR. HARRELL: I vote no, because I'm not impressed with the data, the available science that has been presented today, and also I consider that, even though we should not expect a zero risk, that we are not in -- we are in a position where we don't have to take any risk at all.

CHAIRMAN BROWN: Thank you. Peter.

DR. LURIE: I vote no as well. The risk is so small as to be almost impossible to quantify. Yet as pointed out, it can be reduced to even closer to zero with no detrimental effect upon the American public health that I can see. Therefore, I vote no.

CHAIRMAN BROWN: Doris?

DR. OLANDER: I vote yes for the particular reason that we would drive reporting of the disease underground in other countries.

CHAIRMAN BROWN: Beth?

DR. WILLIAMS: I vote yes. I think that the evidence that's been presented suggests that there's an insignificant risk, but especially I believe that having a blanket policy isn't going to serve the public. So I think we would need to reevaluate some of the uses of these products.

CHAIRMAN BROWN: Well, the nos have it, six to five, which eliminates question 2.

Question 3: Same question with respect to tallow derivatives. The tallow derivatives, you recall, pass through or we can stipulate that they pass through, if there's any question, just to be sure that no opening is left, that we can specify that tallow derivatives are processed through the minimum heat/pressure conditions that are known to inactivate the agent.

I think we were presented with information which indicated that this was 100 percent the case, but I think I would like to be assured that that is 100 percent the case. That is, every tallow derivative has gone through a temperature of at least 132 degrees Centigrade under three bars of pressure for at least 20 minutes.

DR. OLANDER: Question. How many strains of these agents have been tested at 133 20 mins 3bars?

CHAIRMAN BROWN: Quite a few. The BSE -- Apparently, there is only one strain, but many strains of scrapie, many strains of CJD, transmissible mink encephalopathy and kuru. I think everything has been -- if not 3bars, everything has been checked through at least 121 to 134 degrees in an autoclave situation.

It's been found that 121 has sometimes complete activity, occasionally incomplete activity,

but that 134 at 3bars for 20 minutes -- and David, you may now think that an hour would be better, but at least 20 minutes. I think most of the processes we've seen go at least an hour anyway and two and three hours and sometimes longer.

DR. OLANDER: I was just wondering where we -- how we could get scientific to set a benchmark.

CHAIRMAN BROWN: This is a -- Probably if there is any consensus about the inactivation of these agents, it's that the best known inactivation to date, and it is virtually 100 percent without failure is this method of steam under pressure heat.

DR. SCHONBERGER: Let me preface my comment, now that I'm on the derivatives. I'm leaning on the other side of having the FDA regulations changed to loosen it, because I was impressed with the procedure, the harsh procedure this has gone under and the inactivation that would result, and that we're dealing with a very insignificant risk. But at the same time, Paul, I think it was you that mentioned that the inactivation procedure was under a dry condition and that that was somehow different from the studies that have really been done to show the effect of heat on the agent.

CHAIRMAN BROWN: Yes. The derivatives, I

think, don't quality for that. That is, they are under pressure as a liquid with that heat applied to them as a liquid under pressure.

DR. SCHONBERGER: Good.

CHAIRMAN BROWN: Larry, your vote?

DR. SCHONBERGER: You want to clarify what the meaning of the yes and no is, so we --

DR. GREEN: The one thing I would say on derivatives, I know of nowhere you can make derivatives without exceeding the minimum of the three bars 133 degrees C. in 20 minutes.

CHAIRMAN BROWN: Right. In other words, what we're talking about is, if you had to design an experiment to inactivate these agents, you would design a derivative process.

DR. SCHONBERGER: Do you want to clarify what the meaning of the yes and no is?

CHAIRMAN BROWN: Again, it's the same thing. No means we leave everything intact and leave this rigorous exclusion of BSE or BSE status unknown countries as verboten. A yes means that we recommend that the FDA change their posture and relax it.

DR. SCHONBERGER: Okay. Well, unlike the plain tallow, I think that the tallow derivatives have an insignificant risk and, therefore, I vote yes.

CHAIRMAN BROWN: Leon?

MR. FAITEK: This is a little tougher question, and I agree that this is a relatively safe product. All these products are relatively safe.

I will, nevertheless, vote no, because I don't want to get into these other issues.

CHAIRMAN BROWN: Mean logic? Ray?

DR. ROOS: I vote yes. I think the inactivation step here is a very important one. So that, assuming we are dealing with infectious material or some breakdown in processing or some -- you know, if the BSE curve begins to go up rather than down, I feel confident that the risk here is smaller than in the first situation because of the inactivation step. So I vote yes.

CHAIRMAN BROWN: Bill?

DR. HUESTON: Yes.

CHAIRMAN BROWN: Linda?

DR. DETWILER: Yes.

CHAIRMAN BROWN: I vote yes. Don?

DR. BURKE: I vote yes as well, but I think it is a little more complicated, that there are many different types of derivatives that are not all necessarily, as I understand it, through the high temperature and pressure, and we do need to consider

them one by one.

CHAIRMAN BROWN: Barbara?

DR. HARRELL: No.

CHAIRMAN BROWN: Peter.

DR. LURIE: I agree that the risk in the previous question was small and that it is now smaller, but I still fail to see the benefit of changing the regulations or the guidance. So I vote no.

CHAIRMAN BROWN: Doris?

DR. OLANDER: Yes.

CHAIRMAN BROWN: Beth?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: The yeses have it, the tally being eight to three, which means that we have to consider question 4. I would propose that the committee, to make their life easier --

DR. HUESTON: To have the break before we discuss it. Thank you.

CHAIRMAN BROWN: Exactly. So that way any last minute lobbying can also occur. We will reconvene at eleven sharp.

(Whereupon, the foregoing matter went off t he record at 10:42 a.m. and went back on the record at 11:02 a.m.)

DR. FREAS: Would you take your seats, please. If there is a Dr. Mara Ricketts in the audience, I have two urgent packages. They will be out on the table outside the room, if there's a Dr. Mara Ricketts here. These are two packets marked "Urgent."

CHAIRMAN BROWN: The committee has opened up a discussion of question 4 in which we are going to recommend to the FDA to make one or more changes in their current policy. I think the first thing I would like for the committee to hear is just a very summary recapitulation from Dr. Green, if he is here, on the process or alternative processes for, first, saponification and, second, derivatization; but the first, saponification.

DR. GREEN: Well, in saponification you use a minimum of 12 moler caustic. Actually, most people use 50 percent caustic solution. That is a standard commodity that's sold in industry, and the less water you put in, the less water you take out.

So when you start saponification, you normally use 50 percent caustic. There would be possible some small formulators that might not want to go to 50 percent, but the majority of the industry always starts with 50 percent caustic, because it's

standard in our plants for many, many reasons.

It's less water in. It's less water out. It costs money to take water out of the finished product. You're taking your saponification up. Actually, the lowest temperatures in which you're doing saponification for soap making, as I said yesterday, there are no fatty acids produced in this country from saponification; because you would have an actual salt formed, and then you would have to add either one of the three mineral acids, either hydrochloric or sulfuric or phosphoric, to neutralize off the alkali.

This would then require you to filter it. You would lose 15-20 percent of your throughput. Then you would never get below the five part per million of requirement to have in a fatty acid -- no more than five parts per million sodium ion, because in derivatizing the fatty acid to other derivatives, whether it's oxalkylation or what have you, the sodium ion interferes with this reaction, and very few customers -- that's respect to setting a standard -- they will not allow you to exceed five ptm.

So you cannot produce fatty acids via the saponification. I know of no company that does it, and I am familiar with every single manufacturer of

fatty acids in the United States.

CHAIRMAN BROWN: And then the second part, the derivatization always involves at least -- at least 20 minutes of at least 3 bars of at least 132 degrees Centigrade.

DR. GREEN: Yes, they do. Then if you're dealing with the fatty acid itself and your derivatizing that, it will take you at least an hour, and you will exceed the three bars, and you will exceed the 135 degrees C. There's no way you can make any of those derivatives, with the exception of the calcium stearate, but that calcium stearate has gone through two processes to get to the stearic acid that went through over 250 degrees C and, as we said, over 700 psi to get there up the distillation tower.

CHAIRMAN BROWN: Right. Thank you. Is the committee clear about that? Also, when we're talking derivatives, we're talking --

DR. BURKE: I'm not quite clear yet. When we talk about derivatives, that they can either go to be saponified and then to be derivatized after that or that they go one way or the other?

DR. GREEN: No. In derivatives -- The only saponification that's really going right now is soap manufacturing. All the derivatives are now

produced by the free fatty acid, and there has been a massive consolidation in this country in the past 20 years.

I know -- I was originally with a small company many years that was bought by Witco, and Witco had acquired a massive number of companies. There's been 16 consolidations by our company alone. So I know when I say nobody is doing it, and that's how it's done.

DR. BURKE: But when we talk about derivatives, we're also -- The broader term here includes the saponified materials, because that isn't tallow.

DR. GREEN: Yes, it is tallow, and it is saponified, but even if you -- in the soap making, which is a multi-step process, it's not a single step. IN the drying stage in removing of the moisture in the soap, you actually exceed the 135 bars.

DR. BURKE: So my question to the Chair then is are we including in this -- in our discussion of derivatives, do we also include in this the discussion of saponified tallow?

CHAIRMAN BROWN: Well, evidently. Soap is not considered a derivative, according to the charts. Soap and soap products are not under the aegis of

derivatives.

DR. BURKE: so are we not going to discuss the saponified at all?

DR. CHIU: Soap is not regulated by FDA. But the glycerin generated upon saponification would be regulated by FDA.

CHAIRMAN BROWN: But would that be considered a derivative?

DR. CHIU: Glycerin is a derivative.

DR. GREEN: It would be considered a derivative, but in the distillation of the glycerin from crude glycerin, as I showed yesterday, it's a two-step distillation, and it far exceeds the temperatures of the 133 degrees C and three bars, although in distillation of glycerin you do it at reduced pressure. Otherwise, you'll polymerize the glycerin.

DR. BURKE: I think I understand. We are not going to discuss soaps.

CHAIRMAN BROWN: Well, I don't know. Soap is considered -- We're going to get some advice on the FDA as to what they want to consider.

DR. HUESTON: It's not coming from the FDA. It's not regulated.

CHAIRMAN BROWN: Oh, well, it's not

regulated. Okay. So the entire soap industry is not under the purview of the FDA.

DR. LAMBERT: Lark Lambert, Office of Cosmetics and Colors. Soap as soap is not regulated, but soap, if it has moisturizing or if it has a cosmetic claim --

CHAIRMAN BROWN: Glycerin is regulated.

DR. LAMBERT: Right, but if you say on a soap that it moisturizes, then it becomes a cosmetic. If it's just soap, it's not regulated.

CHAIRMAN BROWN: Okay. Again, Dr. Green, the distillation procedure that produces the glycerin that goes into soap -- it's a two-step procedure?

DR. GREEN: Yes.

CHAIRMAN BROWN: And the temperature exceeds 132?

DR. GREEN: Yes.

CHAIRMAN BROWN: But it's done under negative pressure, is it not?

DR. GREEN: Well, it's done under negative pressure, but the temperature is about 250C and not 133.

CHAIRMAN BROWN: Right. So we've got a circumstance where the temperature is double what it would be if under pressure, only it's not under

pressure.

DR. GREEN: We do it under reduced pressure, but you're taking the moisture out. So it is not a dry heat. It is a wet heat.

CHAIRMAN BROWN: No, that's understood. It's a wet heat, not under positive pressure at very high temperatures. That's glycerin, and the derivatives as such, which you see on the chart here, are all subject to pressurized high temperatures for length periods of time. Everybody clear about that?

We're not talking about soap at all, only to the extent that it would contain glycerin or -- well, glycerin. Yes, Barbara?

DR. HARRELL: Is Dr. Green speaking for the BSE countries or just for the United States processes?

DR. GREEN: Strictly for the United States processing, but I'm quite familiar with all the processes, since we are a multi-national company, and I deal with multi-national companies.

DR. HARRELL: So what you're saying is -- So it would include BSE countries?

DR. GREEN: Glycerin -- All glycerin anywhere in the world is recovered the same way. You have to distil it. You can't get it pure any other

way. You can't get the water out.

DR. HARRELL: You would distil it, but would you do it at the same temperatures? Would you do it under the same pressure and time constraints?

DR. GREEN: You would do it under vacuum. Otherwise, you lose the glycerin. It polymerizes very easily, and we actually make product by polymerizing glycerin. So we know how easy it is to polymerize it.

DR. HARRELL: But still, is it the same temperatures, the same pressure?

DR. GREEN: All companies, regardless of whether they do it within ten degrees, operate the still the same way. You have slight design differences in distilled, but they're plus or minus ten degrees. They're around the same.

CHAIRMAN BROWN: Thank you, Dr. Green.

DR. OLANDER: One last question, Dr. Green. On page 6 or 7 on your glycerin distillation, you said just now that it was 250 degrees. It says 166 to 175.

DR. GREEN: Well, I'll correct that. I didn't have my slides with me.

CHAIRMAN BROWN: Well, we have a number of changes that we can consider. I'm not -- Maybe I can again make an effort. Unless there is further

discussion about the details of what we might wind up doing eventually, I'll offer you a blank proposal for your consideration and vote.

That is that tallow derivatives -- and now we're talking about tallow derivatives, not glycerin -- that tallow derivatives which we've heard all are subject to high pressure, high temperature, long time procedures which are currently not permitted to be sourced in BSE countries, whether they be for injectables, for oral products, for other drug products or for cosmetics, all four of the items that you see across the bottom row -- that they all be allowed. They are presently not allowed.

I would suggest that the committee first vote on whether or not to remove this restrictive recommendation right across the board, in view of the processing that all derivatives go through.

So I'm going to take a vote on that.

DR. BURKE: But your definition here of a tallow derivative is some -- you want to give a more distinctive definition?

CHAIRMAN BROWN: Yes. Whatever is shown on these two charts in the box derivatives, and they've all gone through this temperature/pressure/time process, every one of them.

So there's not an alternative here in terms of processing. They've all gone through heat, pressure, time that has been demonstrated to be an effective sterilizer of this group of agents.

DR. HUESTON: You're excepting or including glycerin? I'm sorry.

CHAIRMAN BROWN: No, not considering glycerin now. Glycerin apart. We'll take up glycerin next. Now to try and make our job a little easier, I'm talking about only those products which have been subject to high pressure, high time, high temperature.

DR. ROOS: Just so I understand, Paul, maybe it's taken for granted. The source material is not a neurologically ill animal?

CHAIRMAN BROWN: Yeah, I think that's understood. That's implied.

DR. ROOS: And there are particular slaughter house procedures that are in effect in BSE countries that relate to removing brain and spinal cord first. Is that right?

CHAIRMAN BROWN: Well, let's find out. Would it be possible for spinal cords and brains to be amongst the materials which would be saponified or used in -- not saponified but used as derivatives -- as source material?

DR. BRADLEY: Since there's no -- If we're talking about European Community alone, since at this present time there isn't a specified risk materials ban, that ban is -- If it exists at all, it's related to the specific governments.

As far as I'm aware, all the governments of countries which have native born cases of BSE operate such a ban. So that the ante mortem inspection/post mortem inspection and removal of brain or skulls and spinal cord actually takes place in most countries, but not necessarily in the other countries of the European Community which have not reported a case of BSE.

CHAIRMAN BROWN: Right. So that they would not be, according to the USDA, considered as BSE positive countries.

DR. BRADLEY: Precisely.

CHAIRMAN BROWN: So again --

DR. DETWILER: We changed the policy. Now all of Europe is actually treated equally.

CHAIRMAN BROWN: As BSE positive?

DR. DETWILER: As BSE risk until they complete the risk assessments, but right now it's the entire.

CHAIRMAN BROWN: Well, let me amend the

proposal then, which I think would be along the lines, Ray, that you suggested, and propose a blanket change to yes and stipulate these conditions of the removal of either the head and the brain or brain and spinal cord and pre- and post-mortem inspection of the animals.

In other words, with those conditions, setting those conditions, then we allow European source material to be used for derivatives. That's the proposal on the table.

DR. HARRELL: Dr. Brown, would that be implied that the spinal cord is intact?

CHAIRMAN BROWN: What do you mean, intact -- what? Taken out. It's removed. It's gone. It's not part of the material. The spinal cord and brain are not part of the input carcass. Spinal column. Spinal column and either brain or head, whichever they choose to remove. I beg your pardon?

DR. HONSTEAD: The spinal column is the bones, and the spinal cord is the nervous tissues. So you want the spinal cord -- the spinal column, the bones, including the cord or just -- The SRM ban is the cord.

DR. BRADLEY: Yes.

DR. HONSTEAD: They're removing the spinal

cord after they split it.

DR. SCHONBERGER: Right. Maybe Ray should describe what the system is.

DR. BRADLEY: It could be helpful to use one of the slides I used yesterday of the EU proposal.

At this point in time, there is no European-wide specified risk materials ban in operation, but there is a ban in operation, obviously, in the UK and in all those countries that have actually had cases of BSE in native born animals. But there are countries in Europe which have neither a ban, but they have had cases of BSE in imported animals.

CHAIRMAN BROWN: Yes, I understand. I think it would be too complicated -- I understand what you're saying. Go ahead.

DR. BRADLEY: But on -- The list that was proposed to be operative from July last year is on the board. So it would be the skull, including brains and eyes; tonsils and spinal cord from all cattle greater than one year old; and from sheep and goats also over one year old, plus the spleen from sheep and goats, plus the vertebral column from those specific species would be prohibited but only from making mechanically recovered meat.

In the present context, we're looking at the top three items, but I repeat, this is not in operation throughout the European Union; but a ban such as that does operate in all the countries with BSE in native born animals. The precision of that in relation to what's written on the chart there has to be clarified with the governments concerned.

As Linda pointed out, it is sometimes difficult to be absolutely precise in how they apply their ban. Until it is a Union-wide ban, I can't really speak for each individual government.

In the UK we've got tougher rules than that. We take heads out, as an example, rather than just the skull.

CHAIRMAN BROWN: But the committee can stipulate that the European Union that -- that this restriction would apply not on a country by country basis, but as a blanket basis. That is that we will accept this material if SRM are not a part of the input rendered material.

DR. DETWILER: May I suggest one modification, if we do stipulate, if we would do like either skull or brain and spinal cord, but not tonsil, because it's -- To my understanding, in cattle there's been no evidence of infectivity in tonsil. Is that

correct?

DR. BRADLEY: That is correct.

DR. DETWILER: And I can tell you only from somebody who has taken out now about 1,000 tonsils, it's no easy task.

CHAIRMAN BROWN: Would it be acceptable then to ask for this blanket change and simply say from cattle in BSE positive countries that have had their brains and spinal cords removed?

DR. BRADLEY: Mr. Chairman, may I suggest that you include the eyes as well, because we do notice infectivity in the retina.

CHAIRMAN BROWN: Okay.

DR. BURKE: The issue of cord versus column -- my understanding was that there is, not a substantial, but at least relatively high amount of infectivity in the dorsal root ganglia which are not pulled when you do a spinal cord, and that was the rationale for including the column. Is that correct?

DR. BRADLEY: Yes.

DR. BURKE: So there is some additional tissue, and it's a call as to whether or not that extra few grams of tissue makes a difference.

CHAIRMAN BROWN: Any feeling from the committee as to whether vertical column or spinal

column --

DR. HUESTON: Can I ask a more basic science question? Are we hence saying that from the science we believe that this proteinaceous agent can survive distillation and cracking? That's where we're headed.

I mean, I thought maybe you were going to go stepwise toward that point, but isn't there a question first as to whether or not this agent can survive? What we're talking about are pretty darn extreme processes.

CHAIRMAN BROWN: Yes. We have, as far as I know -- and again, Bob can tell me if I'm wrong. I know of no published or unpublished report of this agent surviving this treatment.

DR. ROHWER: Bob Rohwer, VA Medical Center, Baltimore.

I would agree with you, and especially when alkali is involved. It seems very unlikely that these agents could survive this. We have been surprised in the past, and there is one element of this that does bother me.

That is that there is one other ingredient in this triad of temperature, pressure and time, and that is water. There is some evidence, both from

David Taylor's work and some of the things that I've done and you've done, actually, Paul, that dry heat is very ineffective in killing these agents.

So I wonder if, under these anhydrous -- just how anhydrous these conditions are, and whether in the end it shouldn't -- It seems very unlikely that things would survive, but I'd feel a lot more comfortable to actually see it validated as a consequence of that.

It's a condition that could be included, I suppose, in these recommendations. But in terms of aqueous conditions, indeed, I don't know of any situation in which this stuff would survive.

DR. HUESTON: Well, I'd love to have a flow chart that shows this, but if we talk about fatty acid splitting, what it starts with is tallow and steam, if I followed the presentation correctly. So you're taking three to four hours at 248-271 C. at pressure of 710-730 psi, with steam, with live -- That's wet heat, isn't it?

DR. ROHWER: I think that it would be nice to have Dr. Green clarify that.

CHAIRMAN BROWN: He's right behind you.

DR. ROHWER: Yes. Okay. The other thing that wasn't clear to me in his earlier presentation is

I'd still like it stated in a totally unambiguous way that everything that goes to derivatives has gone through the saponification process first.

DR. HUESTON: Yeah, and if that's not true, but --

DR. ROHWER: That's what the chart says up here.

CHAIRMAN BROWN: No, but not for the edible. The edible doesn't show saponification as a first step.

DR. HUESTON: I think it would be ideal if the chart was -- we took it one step further and just made that flow, because I think we're losing some people as to which goes where.

CHAIRMAN BROWN: Right. Dr. Green.

DR. GREEN: The conditions apply both for edible and nonedible. They go through -- and when we're talking about steam, there's three types of steam. There's low pressure steam. There's mid pressure steam, and there's high pressure steam.

This is high pressure steam. You actually counterflow the tallow. Counterflow is against high pressure steam. When we talk about water in there, that's -- water comes out with the glycerin, but when the two are intimately contacted in the reaction, it's

high pressure steam at those temperatures, and that's why it's expressed that way.

There isn't any fatty acid produced in this country via saponification. All of it is produced either by transesterification or by the splitting or what we call hydrolysis. That is the only two methods that any tallow fatty acid is produced in the United States today, period.

DR. HUESTON: And this countercurrent steam process at the beginning of it, there's a lot of water there.

DR. GREEN: Well, yes, but --

DR. HUESTON: At the beginning.

DR. GREEN: -- what I'm saying is that we inject steam at the top, and we inject the fatty acid at the bottom of the reactor tube, and they pass each other; and, yes, it is condensed down to water as the steam reacts with it, but the temperature is still maintained at the temperature and pressures I presented in the chart.

CHAIRMAN BROWN: What I'm getting at is trying to answer Bob's question about the aqueous.

DR. GREEN: Yes, it is water.

CHAIRMAN BROWN: At the beginning, it's aqueous. So live steam is going through a solution

that could be considered aqueous. At the end, it's less aqueous.

DR. ROHWER: Probably the most relevant thing is it's hydrolytic, and that's probably the crucial feature of the chemistry in terms of inactivating these agents.

DR. HUESTON: So those tallow derivatives that flow from the initial process of hydrolysis would go through this wet heat treatment initially, and then go to further cracking on down the line.

DR. GREEN: That's right.

DR. HUESTON: Now how about those derivatives that go through transesterification? You talked about time and temperature. Is there -- Help me understand. From raw tallow through transesterification to tallow derivatives, is there a wet heat treatment there?

DR. GREEN: Yes, there is some wet heat in that. It is not to the extent that you do, but you have methyl alcohol in there, and you're forming a direct transesterification with methanol and replacing the glycerin with methanol at those temperatures and pressures.

Then they further do that, but prior to that there is a partial hydrogenation that is at

rather high temperatures and a fair amount of time involved there. You do have to do a partial hydrogenation.

We -- The industry -- this is across the board. There is a slight partial hydrogenation of raw tallow before we ever go through the splitting process. We do this because it makes the unit run smoother, and you get a more efficient yield out of your process.

DR. HUESTON: But that's just hydrogen, not steam. Right?

DR. GREEN: Yes. That's just hydrogen, but I'm making a point. You do a partial hydrogenation prior to going to either one of these reactions.

CHAIRMAN BROWN: Is the committee clear? Okay. Now you wanted, Will -- Thank you, Dr. Green. We may call you back.

Will, did you want to --

DR. HUESTON: I was just suggesting, for those -- As an example, to sort of help us, for those things that go through this process of hydrolysis, fatty acid hydrolysis, the splitting, and then go to the derivatives from that beyond that, I'm asking the question: Is there anyone here that thinks, that

believes that the agent can survive that; because if not, then our discussion is moot. You follow me?

CHAIRMAN BROWN: Yes. No, I follow you perfectly, and the implications of what we would be voting on would be, no, this process is a 100 percent killer, but just in case it isn't, we'll take the spinal cord and brain out. I mean, that's the logic of that particular vote.

Sometimes we vote without perfect logic, actually.

DR. HUESTON: Let me ask, did anybody ever take the BSE agent through from this beginning step and look for what happened to infectivity?

CHAIRMAN BROWN: Validation through a derivative?

DR. HUESTON: Yes.

CHAIRMAN BROWN: I don't think so. David, there's been no validation studies on a derivative, have there?

DR. TAYLOR: Certainly, not published, as far as I'm aware.

DR. HUESTON: It's pretty -- Well, I was going to say, it's pretty tough since you can't find it in the tallow, to begin with. If you can't identify it in the raw material going in, how are you

going to identify it in the raw material coming out?

DR. ROOS: Let's spike the tallow going into the derivative and --

CHAIRMAN BROWN: Yes, you can imagine all kinds of validation tests, but I think Will's point is well taken. If you can't find it in the input, to begin with in reality, and then put it through a process that is about as good as you can imagine to kill it if it were in there, I'm not sure that anybody would care to spend the time or money to try and validate the procedure.

I mean, it's been validated so many times in the laboratory, not using tallow, for sure, but even so -- I mean, the temperatures, times and pressures that are being used on all these derivatives we don't achieve in the laboratory, and yet we get total kills. So personally, I'm totally comfortable with this procedure as a killer.

DR. ROOS: So that's been validated with the BSE.

CHAIRMAN BROWN: Right.

DR. ROOS: This temperature or comparable temperatures and pressure.

CHAIRMAN BROWN: David, you've done that. BSE has been one of the agents used in an autoclave

style experiment. Right?

DR. TAYLOR: Yes.

CHAIRMAN BROWN: No -- Yes?

DR. WALKER: Paul, I just wanted to point out that in terms of the reaction sequence of making various derivatives from fats, there was a flow sheet that was provided to the Advisory Committee yesterday, a one-pager, which provides that flow in terms of reaction to form saponification or hydrolysis or transesterification. So that should be in your paper work that you have with you.

CHAIRMAN BROWN: It's just that it's been growing by about two pounds an hour.

DR. WALKER: I understand.

CHAIRMAN BROWN: If you would like to come up and find it -- Yes?

DR. ROOS: I guess another issue has to do with regulation of this process itself and how confident we are that, in fact, all of the processors will follow these safety regulations in an appropriate way.

Now maybe there's no way to get this processed tallow except by inactivating it. So I just wonder whether I can have some assurance there. If in fact, people say there's no way that this agent could

survive, given this, sounds good to me; but I'm just worried about the controls here.

CHAIRMAN BROWN: Yes. You're worried about what they call good manufacturing processes.

DR. ROOS: That's why, you know, we've always come back to the source material as being important. Now maybe we don't want to be quite as stringent as the original suggestion, but I still want to return to the confidence that everything is going to follow what everybody believes is going to be 100 percent inactivation.

CHAIRMAN BROWN: Yes. For this I turn to the FDA proper. I assume that any recommendation you make includes some stipulation that what you are recommending is, in fact, carried out.

DR. CHIU: As Kiki mentioned earlier, recommendations are different from regulations. Recommendations is the best current thought of the agency. We recommend to industry, and it's not enforceable. It's not like regulations. Then it's law. You have to follow.

CHAIRMAN BROWN: So there are no guaranties, Ray, until it gets past the guidance -- them one, recommendation; two, guidance; three, law phenomenon, but it is, I think, understood that good

manufacturing practices become a part of this as it goes through this procedure, and it's something that we probably shouldn't concern ourselves with other than to have it on the table that we think that this is, obviously, a part of the whole package.

We could then vote on one of two things. We could vote on the original proposal that I made, which was unrestricted use of derivatives. That is, unrestricted in terms of the source material, including anything which went into the bin; or we could vote on a proposal that is a little more stringent, saying that this is okay as long as brains and spinal cords have been taken out.

Would the committee like to vote on either one, neither, both? Yes.

DR. OLANDER: Question. We have several options when we get to the head. We have the whole head, the skull and eyes or the brains and eyes.

CHAIRMAN BROWN: Yes. Well, the first decision, I guess, is to whether or not -- Why don't I just not ask the committee but ask the committee to vote on the original proposal, which has nothing to do with what tissues are going into the mix, simply these derivatives may come from BSE positive countries or, to rephrase it in terms of question 4 which was voted

yes, that the alteration will be that derivatives may be sourced from BSE positive -- from any country, irrespective of BSE status. I think that's the question on the table.

Derivatives, derivatized products made from tallow may be sourced from any country, irrespective of BSE status.

Larry?

DR. SCHONBERGER: I'm in agreement with that.

CHAIRMAN BROWN: I'm sorry?

DR. SCHONBERGER: I'm in agreement.

CHAIRMAN BROWN: Okay. Leon?

MR. FAITEK: I vote no.

CHAIRMAN BROWN: All right. Ray?

DR. ROOS: I guess I have this continuing problem with the source material being central nervous system material from BSE address countries. I'm not sure that I would get involved with all countries in the European Union, but I do have a problem with that source material. So I'm --

CHAIRMAN BROWN: Okay. The vote is?

DR. ROOS: So is that a no?

CHAIRMAN BROWN: No. Bill?

DR. HUESTON: Yes.

CHAIRMAN BROWN: Linda?

DR. DETWILER: Yes.

CHAIRMAN BROWN: I vote yes. Don?

DR. BURKE: I vote no, because I see no advantage of including known risk materials, and there are several types of inactivation that we're talking about here. I think it's still too early to wave a blanket and say that they're all equally effective in activating the agent. They include saponification, transesterification, hydrolysis, and a number of techniques, and unless I'm sure which process we're talking about, I don't want to vote yes.

CHAIRMAN BROWN: We are talking about high pressure, long time, high temperature, aqueous solutions for the derivatives. You can forget about saponification.

DR. HUESTON: We excluded saponification.

DR. BURKE: Well, there are still two other major techniques, as was pointed out, transesterification and hydrolysis, and I'm still not sure that they all include a high water -- a high proportion of water in the process; and if it's dry, I'm not sure that that's inactivating. I'm sorry. I'm still a little -- enough confused in the process. I'm not sure that all of the products that we're

talking about meet those characteristics.

CHAIRMAN BROWN: Barbara?

DR. HARRELL: No.

CHAIRMAN BROWN: Peter?

DR. LURIE: No.

CHAIRMAN BROWN: Doris?

DR. OLANDER: Yes.

CHAIRMAN BROWN: Beth?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: Yeses carry.

DR. SCHONBERGER: What was the vote?

CHAIRMAN BROWN: I'm sorry. The vote was six to five. That concludes tallow. Thank you very much, committee, a very tight deliberation.

Now we go on to the question of gelatin.

DR. ASHER: Good morning. You are to be commended on your strength in being able to stay engaged after this morning's difficult deliberations.

This is new-variant CJD, something that all of us, regardless of our opinions on some of these topics, would very much like to keep out of the United States.

I'm David Asher from the Center for Biologics Evaluation and Research, and I've been asked to revisit with you the topic of an advisory committee

meeting that was held almost a year ago and, of course, continuing yesterday's discussion on the safety of gelatin and gelatin byproducts derived from potentially TSE agent contaminated sources.

I'll review for you briefly the reasons for the meeting last year, the advice that the committee offered to the FDA, of course, filtered through my own perceptions, guidance that the agency issued later last year, responses to that guidance, additional concerns of the FDA now, and then I'll introduce you to the charge and two specific questions that we have for you today.

In 1993, as you've heard, FDA requested that bovine materials from animals identified by the USDA as BSE countries not be used to manufacture FDA regulated products intended for humans.

The following year, the agency explained that it did not object to using bovine derived materials from BSE countries to manufacture pharmaceutical grade gelatin, although it considered it prudent to obtain all raw materials from non-BSE countries, and that we referred to as a so called gelatin exception.

The exception from sourcing recommendations reflect that a conclusion by the

agency that available evidence did not suggest transmission of TSE agent by gelatin based on an assessment that manufacturing conditions for gelatin were likely to inactivate the agent, and there was an implicit reliance on a perceived species barrier between cows and humans to protect humans, just as the species barrier between sheep and humans were thought to have protected us from scrapie; but recognition in the UK of a new spongiform encephalopathy in cats, a species not previously known to get scrapie, suggested that the BSE agent might have a broader host range than did the scrapie agent, and that it was probably spread to cats by food.

The recognition, of course, in March of 1996 of new-variant CJD reduced further any remaining confidence that the species barrier provided absolute protection to humans from the BSE agent.

Because experimental data submitted to the FDA failed to show that gelatin processing removed all TSE infectivity from the starting materials, and we still have not received data showing that, and because the agency was concerned that some source materials for gelatin might contain neural tissues of cattle from BSE countries, last year we asked the TSE Advisory Committee to consider the issue of TSE and

the safety of imported of imported gelatin and whether the gelatin exemption was still justified.

Policies of international authorities on the safety of gelatin from BSE countries have been somewhat inconsistent. A WHO consultation last year concluded that careful selection of source materials is the most important criterion for safety of medicinal products, including gelatin, and that a manufacturing process utilizing production conditions demonstrated to remove or inactivate -- significantly remove or inactivate infectivity from source materials should be used. If so, gelatin is safe for all purposes.

The most recent chapter of the OIE noted that gelatin from BSE countries, as well as tallow, are considered to be safe if produced by processes under study which inactivate any residual BSE infectivity, implying that a manufacturing process should remove all the infectivity potentially present in starting material, if the product is to be considered safe.

Of course, last year's EC decision, again postponed except in the UK, prohibiting use for any purpose of specified risk material did not except gelatin.

The USDA has been considerably more cautious in assessing the potential risk to U.S. ruminants posed by imported gelatin. So in December 1991 USDA ruled that gelatin from BSE countries is not to come in contact with ruminants, explaining the following year that gelatin derived from ruminants from BSE countries, of course, poses a risk of spreading BSE to ruminants.

So almost a year ago we convened a meeting of this committee to consider the safety of gelatin, reviewing the sources of starting material, processing conditions -- that is, the potential to remove or inactivate the agent -- validation of those processing conditions -- the actual evidence that the process cleared TSE agents -- and finally, providing an assessment of the overall risk to humans caused by gelatin, imported gelatin and gelatin byproducts, especially the potential for an exposure sufficient to transmit infection to humans by various routes of exposure, including the amount of infectivity likely and other factors.

The TSE Advisory Committee offered the following advice. This, of course, is an abbreviated summary, and a full transcript is available to those who have an interest in it.

One: Current scientific evidence no longer justifies excepting gelatin from restrictions recommended by the FDA for other bovine derived materials originating from BSE countries.

Second: The USDA BSE list should be expanded to identify countries that, although not reporting BSE in native cattle, have surveillance systems that are inadequate to assure that BSE is not present, and such countries of unknown status, of course, are to be considered less reliable sources of bovine derived material than BSE free countries where there is an adequate surveillance program.

Bovine gelatin administered parentally poses a greater risk of transmitting TSE to humans than the same product would ingested.

Four: Brains and spinal cords of cattle from BSE countries should be excluded from raw materials used to produce gelatin for human consumption.

Alkaline processing with lime may reduce amounts of infectious agent in gelatin, but has not been demonstrated to eliminate infectivity completely, and acid processing is even less effective.

Other steps in the manufacture of gelatin, including degreasing, neutralization with sodium

hydroxide, filtration, deionization, heat sterilization, might also reduce levels of infectivity, but they cannot be relied upon until actually validated.

Finally, better validation studies are needed, and porcine gelatin, pigskin gelatin, poses no known risk of transmitting TSE to humans.

Last fall the FDA issued Level 1 guidance for industry. Again, this is my abbreviated summary of that guidance to facilitate today's discussion.

Repeating from yesterday, first to determine the tissue species and country source of gelatin raw materials; second, bones and hides of cattle showing signs of neurological disease, should not be used to manufacture gelatin.

Gelatin from bones and hides of cattle from BSE countries or countries of unknown BSE status according to OIE standards -- and we did that because the USDA has not yet revised its own standards; there were no other generally accessible standards that we were aware of, and we were not in the position to try and establish our own standards for what constitutes a reliably BSE free or negligible risk country. So we referred to the OIE standards -- should not be used in injectable, implantable or ophthalmic products.

However, at this time FDA does not object to oral and cosmetic use of gelatin from bones of cattle from BSE countries if the cattle were -- and we added some precautions -- from BSE free herds, and if heads, spines and spinal cords were removed directly after slaughter.

Please note that the specific mention of spines in addition to spinal cords was intentional, and was motivated by a concern about probable compliance with simple removal of the spinal cord, the United Kingdom having reported problems with compliance in spinal cord removal as late at least as 1995. So that's what motivated that additional precaution.

FDA also did not object to bovine hide gelatin for foods and cosmetics if hides of cattles with sides of CNS were excluded -- That, of course, was a general suggestion -- and if contamination of the hides with CNS and eye tissues was avoided, or to the use of any bovine gelatin from United States animals or animals from other BSE free countries.

Finally, we did not object to the use of pigskin gelatin, if uncontaminated with bovine materials from BSE countries or countries of unknown status.

We have received 11 thoughtful comments from industry, and I'll summarize for you now several issues mentioned in those comments or in more than one comment, and I trust that presentations from industry later today will expand on those comments and add to them.

First, industry felt that a transition period of at least a year would be needed for industry to implement guidance.

Second, they stressed that the United States absolutely needs bovine gelatin imported from BSE countries to maintain an adequate supply of capsule gelatin for pharmaceuticals.

Third, European slaughterers cannot feasibly remove spinal columns from cattle carcasses.

Fourth, removing spines from carcasses will not significantly improve the safety of imported bovine bone gelatin.

Fifth, we were asked -- The FDA was asked to accept as reliable the assessment - an assessment by the pharmaceutical industry predicting that capsule gelatin prepared from non-UK BSE country beef bones should pose only an extremely remote, negligible risk of infecting human recipients, even if the bones were contaminated with spinal cord, and Fred Bader briefly

presented that same assessment model yesterday.

The risk assessment model used for this prediction has been published and will be presented and compared with other proposed models of risk assessment at the workshop in June that you've heard about several times in this meeting.

As you heard yesterday, the model identifies elements of risk and attempts to assign reasonable values to them, but of course, as you've also heard, not everyone agrees on the appropriate values for the assumptions in the model.

Industry also felt that the FDA guidance unnecessarily shakes public confidence in the safety of imported gelatin, and industry felt that the FDA should have followed notice and comment procedures in issuing Level 1 guidance -- the guidance document of October 7th was Level 1, meaning significant guidance -- on gelatin in the absence of any immediate threat to public health, there having been no case of a spongiform encephalopathy in a human being convincingly attributed to exposure to gelatin from whatever source.

These comments clearly deserve serious consideration, both by the agency and by this TSE Advisory Committee.

Two comments were received from the USDA. An FSIS authority suggested that the FDA should more appropriately prohibit all use in FDA regulated products of gelatin prepared from bones of cattle from BSE countries or status unknown countries, and a colleague from APHIS remarked that the hides of cattle with signs of CNS disease may be considered a safe source of gelatin after a diagnosis of TSE has been excluded by laboratory testing of brains.

We received no comments from consumer groups and no comments from the general public.

New information was published by the UK Ministry of Agriculture, Fisheries and Food, of course, in December of last year, and that, I must say, is of great concern to the FDA and should also be considered by the Advisory Committee.

As Ray Bradley has told you, dorsal root ganglia -- that is, lying within the bone of the spinal column and sternal bone marrow; we are aware that that latter finding requires additional confirmation -- were found to contain infectious BSE agent in cattle experimentally infected by calves.

The MAFF apparently took the findings sufficiently seriously to recommend deboning meat from all bovines in the UK over the age of six months.

The implications for safe sourcing of bovine bones for gelatin seem clear and well stated, I think, recently by the Scientific Steering Committee of the European Union in their February release, and I'll quote here. "So far bones, as a raw material for the production of gelatin, have been considered as a material with no detectable infectivity."

New, unpublished evidence shows that the dorsal root ganglia located within the general structure of the vertebral column, should be considered as having an infectivity for BSE equivalent to that for the spinal cord. As a precautionary measure, the removal of the whole vertebral column other than the coccyx -- I suppose that the oxtail soup industry lobby has struck again -- is now appropriate.

They added that the unpublished information implies that long bones, as well as vertebral columns, must be considered potentially infective, and remarked in general that it is unwise to consider the BSE agent as either present or absent in particular tissues.

I know that last month's SSC position was somewhat more restrained, but their February communication accurately reflects a level of concern

that the FDA shares.

We request now that the TSE Advisory Committee consider this new information as well as the other information to be presented here today.

Finally, as you've heard, responding to recognition of more cases of BSE in native cattle in the Benelux countries, the possibility that cattle from those countries in beef products may have been exported eastward into the rest of Europe.

In December the USDA prohibited importation of all live ruminants and most ruminant products -- of course, excluding gelatin for human consumption because of the lack of jurisdiction -- from all countries of Europe due to the potential risk of BSE.

Taken together this new information calls into question whether any beef bones of European origin can be considered a safe source of raw material for the manufacturing of gelatin intended for human consumption at the moment.

So it seems an appropriate time for the TSE Advisory Committee to reissue the -- to revisit the issue of BSE and the safety of bovine derived gelatin for oral consumption or topical application, remembering injectable and implantable ocular is

already not acceptable, in our view -- that bovine gelatin from BSE and status unknown countries is not acceptable for injectable, implantable and ocular drugs and biologics.

So we now ask the TSE Advisory Committee to consider whether safeguards recommended in the most recent FDA guidance document are still appropriate and adequate to protect the public from exposure to the BSE agent in gelatin for oral consumption or for topical application when the gelatin was prepared from bones and hides of animals born or residing in BSE countries or bovines from BSE status unknown countries.

CHAIRMAN BROWN: Is the word animal there deliberate or should that be bovine?

DR. ASHER: Bovines.

The first question will be: Can healthy cattle from BSE countries or status unknown countries be considered a safe source of bones to produce gelatin intended for oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE free herds and the heads, spines and spinal cords are removed from carcasses immediately after slaughter?

The next question will concern the safety

of bovine hide gelatin. Can healthy cattle from BSE countries or from BSE status unknown countries be considered a safe source of hides to produce gelatin intended for oral consumption -- you all have the question in your handout -- oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE free herds and contamination of the hides with CNS tissue and eyes is avoided?

As always, we welcome any other advice and comments that you have for us, and if anybody has any questions for me, I'm happy to answer them. Thank you.

CHAIRMAN BROWN: Thank you, David.

MR. FAITEK: Dr. Brown, could we have the questions shown on the --

CHAIRMAN BROWN: Well, we're not going to be considering these, Leon, until after lunch, at which time the questions will be up again.

MR. FAITEK: I just want to make sure I have the right questions.

CHAIRMAN BROWN: Okay. You want the upside down slide?

MR. FAITEK: I'll stand on my head for this one.

CHAIRMAN BROWN: The first question related to the safety of bones as a source of gelatin. The second question related to safety of hides as a source of gelatin.

DR. ASHER: Because the additional precautions -- What we attempted to do when the guidance was drawn up -- Because of issues that you'll hear about after lunch, I assume, what we attempted to do was to set up additional precautions that would allow us to have confidence in the safety of gelatin derived from bones of animals in BSE countries. What could we do to increase the margin of safety?

We felt as a minimum that we could require that the cattle be from BSE free herds, and this is for hide gelatin; but for bone gelatin, that BSE free herds, heads, spines, spinal cords removed from carcasses immediately after slaughter, and for hide gelatin, can hides be used if they're from cattle in BSE free herds and contamination with CNS tissue and hides is avoided.

We're only asking for advice on gelatin for oral and topical use again, because we're not entertaining the use of any gelatin from BSE countries for use in any injectable, implantable or ocular drug or biologic or device.

CHAIRMAN BROWN: Okay.

DR. ASHER: And Carol Vincent will review some additional information for the agency after the other presentations, and you'll see the questions again, of course, right before you ask them.

DR. DETWILER: I just want to provide additional information on the Europe situation. The USDA APHIS had come up now with criteria for a risk assessment of each individual country. These are based on the OIE standards for recognition of BSE statuses of countries.

The countries are sent the criteria. They were also sent a questionnaire to go along to answer the questions for the criteria. We are now receiving and have received information from the countries for an assessment.

So some of the countries -- I would expect that not all of Europe would remain in this status shortly.

CHAIRMAN BROWN: What we'll do now during the next hour is have the three presentations in a row before we have lunch, and they will be by Dr. Bradley on the implication of the new BSE data on gelatin; by William Stringer, a safety assessment of gelatin; and by David Taylor about the regulatory policies of the

European Union. Dr. Bradley.

DR. BRADLEY: Thank you, Mr. Chairman. Good morning, ladies and gentlemen.

I would like to again thank the FDA for their very kind invitation to address you on this subject of gelatin, and I commend David Asher's presentation to you, which very clearly put the subject into context.

I think in regard to the safety of gelatin, we need, as with tallow, to consider three things: The source, the process, and the use. My job is really to deal with the source, in particular, in the light of new scientific information.

I think I would like to mention two other important issues to help make the judgment. The first is that, if there was a risk in gelatin, the greatest risk would be to cattle, not to humans, because there would be an absence of a species barrier in the latter case.

The second thing is, in regarding sourcing, by looking purely at the incidence and prevalence of BSE in countries or the unknown status, that is not perhaps the only thing that should be done. You must also take account of the level of surveillance in the countries, the extent and

compliance with the control measures, and their effective enforcement. That equalizes, to some extent, the actual incidence and occurrence, and I think you should take account of those issues.

Could I have the next slide, please.

The aspects to consider are in the raw materials, the processing, and the use. In regard to the raw materials, it's important to assess the species and tissues used, which are bovine and porcine and, for practical purposes, lay only in either -- either in bone or in skin.

Also one has to consider the origin, the geographical origin, of the animals and the instance of BSE in the countries, and this is where I say you need to consider the measures in place and the level of enforcement as well.

The processing involves titer reduction and agent removal, and that will be explained by other speakers, and the use as several factors involved, the dose, the route by which it's administered, and any affect to the species barrier.

Before we start on these studies, it's useful just to look at the more historical studies in regard to infectivity found in bone or skin of animals which have had TSE and which, of course, are food

animals.

First of all, in sheep and goats with scrapie Dr. Bill Hadlow, as I mentioned yesterday, did studies on this natural disease, and there was another study done by another worker in the UK in regard to skin. He found that in goats there was no detectable infectivity in the bone marrow. In sheep, however, in one out of nine sheep and at low titer there was some detectable infectivity.

That was the position of knowledge when we came into the BSE epidemic. In regard to skin, no detectable infectivity was found.

As we then looked at clinical cases of BSE and the tissues from them, we could find no detectable infectivity in bone marrow or in skin. So the natural cases in the field did not exhibit this phenomenon, but in regard to experimental BSE in the preclinical phase, we found no detectable infectivity in the bone marrow or skin, but we did find infectivity in the bone marrow in the clinical phase of disease in one group of animals, and I'll tell you about that in a little more detail in a moment, but it's not been found in the skin in that study. So the skin seems devoid of detectable infectivity.

To remind you again that gelatin comes

either from pigs or cattle and skin or bones -- the next one, please, David -- and that anything that's in red here, other than titles, means potentially dangerous. Anything that's in green is probably safe.

So immediately, if your eye is drawn to something red, it really means danger in some way.

The gelatin risks in regard to sources could be written like this. Currently, uncontaminated porcine skin and bone and bovine skin from healthy animals past fit for human consumption, can be regarded as presenting negligible risk for the production of gelatin, based on the scientific evidence.

Next one, please. Additional guaranties can be provided by using the validated production process in incorporating HACCP principles and by inspection and enforcement.

Now I return to the slide I showed yesterday of the results from the pathogenesis experiment. I want to demonstrate that, in regard to the preclinical phase of disease which commences before the green color, we had infectivity in the distal ileum which doesn't really enter into the gelatin risk factor issue simply because intestines are not used for gelatin manufacture.

Brain, spinal cord, and dorsal root ganglia were found to have infectivity in the preclinical phase in this study, and consistently thereafter. Subsequently, also infectivity was found in trigeminal ganglia which are enclosed within the skull. So they would contribute to infectivity from that source, and also at a later point in time in the frontal cortex.

In this one study, which I mentioned yesterday was uninterpretable, bone marrow was shown to be infective at 38 months post challenge, some three months after the onset of clinical signs in the animals. In other words, in the normal epidemic, if such an animal in that group had been found, it would have actually had clinical BSE, and it would not have entered possibly at all into any gelatin manufacturing process.

I said the experiment was uninterpretable, and I say this wisely. This is what the decision of the SEAC was who considered it carefully. The study is incomplete. In the particular study that we're talking about, we notice that on either side there are no positive results. Mice in those studies are still alive.

Furthermore, there are mice in this study

which are still alive. So there's only a very small proportion of the total that have actually succumbed to disease, but certainly some did.

There are even possibilities that this may be an aberrant result, even from possible cross-contamination, but it is reported honestly as a positive result at this time; but for this collective set of reasons, it's regarded as being uninterpretable at the present moment.

The infectivity risks in bovine bone during the incubation period, the ones which bones could provide source material for gelatin manufacture, would include the skull and the head, and the risk would be from contamination within infected brain, eye and ganglia.

In the vertebral column infected spinal cord and dorsal root ganglia could contribute to any infectivity, but infectivity in other bones would be most unlikely.

Cattle bones fit -- from cattle fit for human consumption could be classed into two groups, skulls and vertebral column, which could be then because of a risk factor be treated and safety disposed of. All other bones could be utilized for gelatin manufacture and, therefore, any use.

Let's consider this in a little more detail. Currently, you could say that uncontaminated bovine bone from healthy cattle past fit for human consumption can be regarded as presenting a negligible risk for the production of gelatin if, firstly, the OIE code recommendations are reducted -- that's an absolute essential -- and the bones are selected on a geographical basis of i.e., freedom from BSE, or -- this is an alternative -- skulls and vertebral columns are removed, or bones only from younger cattle -- for example, under 30 months old -- are used.

The additional guaranties could be provided if a combination of those criteria I've mentioned are used and by using a validated production process incorporating HACCP principles and by inspection and enforcement. Currently, all our gelatin plants are inspected by the Veterinary Service once weekly.

UK gelatin from bovine raw materials for use in food, feed, cosmetics, medical and pharmaceutical products must be prepared from imported raw materials in registered plants with veterinary inspection. If that is done, export is permitted.

That is not to say that, if we chose to produce gelatin from our currently consumable cattle

under 30 months of age from which various tissues were removed, they could not be used domestically; but this would prevent the export of the products containing the gelatin maintained therein.

Thus, for example, if you had that situation of using UK source gelatin, the gelatin was included in the chocolate, we would not be permitted to export the chocolate. Therefore, in practice this is not done. We thus import either the gelatin or the raw materials for preparing the gelatin, and these are prepared in four licensed plants.

Now gelatin for technical, such as photograph use, can use UK sources, and export of that technical material or the technical gelatin is permitted.

I conclude with a situation which one could regard as one of the highest guaranties that could be provided by anyone or any country in the world. Imagine the situation: A feed ban preventing the feeding of meat and bone meal to ruminant animals since 1988, albeit with some weaknesses which have now been corrected; that the gelatin would come from source material from healthy cattle killed in the UK or past fit for human consumption, or under 30 months of age, an age at which BSE is ordinarily rare

throughout the epidemic; no heads or vertebral columns are permitted to be used for gelatin manufacture; no SRM are utilized and are removed from all carcasses.

The gelatin is prepared in licensed premises, using validated procedures and HACCP principles with state veterinary service veterinary inspection. Not only that, the reports of this are published for the public to read once a month to give a reassurance that all the controls necessary are carried out.

I think that gives a very good guaranty myself, but it is the committee's job to assess that, and I haven't addressed the question so much of the European position, but I'm very happy to answer questions, such as I can, on that.

Thank you.

CHAIRMAN BROWN: Thank you. Ray, let's go right on and have all three presentations without any questions. The next presentation is by William Stringer, Coalition of Gelatin Capsule Manufacturers, Thierry Salmona and Reinhard Schrieber, Gelatin Manufacturers of Europe.

MR. STRINGER: Thank you, Mr. Chairman. I'd like to thank the Food and Drug Administration for allowing the Gelatin Manufacturers of Europe and the

Coalition of Gelatin Capsule Manufacturers to make a joint presentation to the distinguished members of the TSE Advisory Committee.

During today's industry presentations, we'll discuss several topics which are listed on this agenda. First, Mr. Thierry Salmona, current President of the Gelatin Manufacturers of Europe, will make a presentation covering gelatin safety as a result of sourcing procedures and the manufacturing process itself.

Mr. Salmona will also present the most up to date results from the Inveresk study, which examined the ability of a narrow portion of the overall gelatin manufacturing process to remove any potential BSE infectious material.

Next Mr. Reinhard Schrieber, Executive Director of DGF Stoess, one of the world's largest gelatin manufacturers, will describe the details of a new study aimed at examining the ability of the entire gelatin manufacturing process to remove potentially infectious material.

Lastly, representing the Coalition of Gelatin Capsule Manufacturers, I will present the capsule industry's perspective on the FDA guidance.

Before I get into that specifically,

however, I'd like to point out the upstream and downstream supply chain associated with gelatin, to make sure that the committee has this clear in its understanding, and where the industry presentations that you're hearing today fit into this supply chain.

The agricultural industry produces cattle which go to a slaughter house, and they do that for the purpose of generating meat for consumption. A byproduct or co-product of that process are bones, and these bones could be used for a variety of different purposes, some of which we've heard of already today and yesterday, such as meat and bone meal; but another application for using those bones is to manufacture gelatin.

So the gelatin manufacturers purchase those bones and produce gelatin. Gelatin, however, has a wide variety of different applications. Gelatin can be used for technical applications such as photographic purposes. It can be used for other industrial purposes.

What we are concerned with today, however, is capsule manufacturers purchasing that gelatin for the purpose of making capsules. So the red line is the part of the industry process you're going to hear about first in today's presentations.

I'll be talking about the blue line, the capsule manufacturers and the production of capsules. It's important to point out, though, that the capsule industry sells those capsules to the pharmaceutical industry, as well as the dietary supplement industry, who then package those products, distribute those to pharmacies and other mass media outlets who then sell the product at a retail level to the consumer.

What I want to make very, very clear is that this is a global process. There are companies who are applying this on a global basis. There's no reason why someone at a pharmacy who is trying to purchase packaged product couldn't purchase that product from someone who manufactured it overseas, for example.

So what we're trying to do in the questions before you today is look at restrictions in only a very narrow portion of the supply chain, and it's important to understand the global nature of this industry.

It's also important to point out differences between this industry and that which you've heard a lot of information about already, the tallow industry. In this industry, we have a shortage of U.S. based bone product that's used to produce

these capsules.

It's also important to point out that, as Dr. Brown indicated at the very beginning of the proceedings here, the Food and Drug Administration takes your recommendations very seriously, as they should. And unlike the situation that you've just considered with tallow, further restrictions on this supply chain could have a very detrimental effect to the finished product that I've shown here at the end due to that shortage of available starting materials.

So I point that out, and I'd just like you to be considering that as you hear the rest of the industry presentations. Mr. Salmona.

MR. SALMONA: Well, good morning. I'm Thierry Salmona. I'm the President of Gelatin Manufacturers of Europe, an organization whose 12 members represent 97 percent of the gelatin produced in Europe, and actually 100 percent of the gelatin which is imported from Europe into the United States of America.

Gelatin, as was described before, is made from three principle types of raw materials, pigskin, bovine hide, and bovine bone. As regard to bovine product, GME undertook a series of initiative to ensure the safety of gelatin made from these bovine

raw materials.

Number one, GME has sponsored independent research to help ensure that in the unlikely event that raw materials from a diseased animal enter the manufacturing process that do not pose a risk to consumers.

All factory -- All ISO 9002 certified, we have all implemented HACCP procedures and analysis in our factories, and all factories are all inspected by official veterinarian services from the various countries and from the European Commission.

A great deal has been accomplished over the last few years. We will describe briefly for you some recently completed research, and also discuss a new study that is currently being initiated. At this time we believe that the data are adequate to demonstrate that gelatin poses no significant BSE risk.

I would like to first outline the steps that are in place to ensure safety of gelatin. I refer to these steps as a safety system, because they are part of the quality system that guides the daily manufacture of gelatin. The system helps ensure that safety is built in so that the reality of gelatin manufacturing process is much safer, that the

conservative assumptions used for purpose of assessing theoretical BSE risk.

We have been given a number by Dr. Bader yesterday, 10^{-12}, as a risk associated to gelatin in the worst case. However, the safety step that we implement in our gelatin factories make sure that these numbers are based on very conservative assumptions and that the reality is always better.

The five steps are represented on this chart and are: Number one, the use of safe animal; the use of safe tissues from these animals; some additional cautions; the process itself, which is bringing some additional safety steps, all of these being guaranteed by traceability, backward traceability and forward traceability, so that we can be confident of sources of raw material which enter the process and their end use in gelatin products.

Each of these steps was factored into the assessment of the safety of gelatin using the PhRMA risk assessment model which was presented yesterday and described to you by Dr. Bader.

The first four steps on this chart are related to safety of the raw material, and I will now go into more details as to that.

Under European regulations, certain

animals are not permitted to enter the food chain, which includes the supply of raw material for gelatin. Excluded in continental Europe are animals from the UK, animals presenting neurological sign, and animal which are not found fit for human consumption subjected to ante and post mortem inspection.

The EU has implemented the BSE surveillance system in countries where BSE cases have been found. Compulsory destruction of afflicted animals and related birds is carried out. Only animals found fit for human consumption after ante and post mortem inspection are used.

This is for safe animals. Moreover, the tissues that we use from these animals are fundamentally safe. Bovine hide and bovine bone have not been found to be infective.

For bovine hide, bovine hide does not pose any problem, does not pose any risk, because we use only hide splits which are not in contact with nerves and, therefore, this product doesn't pose any problem, and this has been acknowledged and recognized by the Scientific Steering Committee.

With bovine bones, there is a risk that neural tissue, which is a high risk tissue for BSE, may be found in connection with the bone. In order to

protect against this, regulations are in place in all countries where native BSE cases have been found, requiring the removal of skulls and spinal cord. This is in place in Europe in all countries where BSE cases have been found.

For the gelatin industry, we remove skulls in every case. Furthermore, there is a stepwise reduction of risk in the preparation of gelatin raw materials. If you look at all this system, there is exclusion of the trace of potentially infected animals. There is exclusion of the trace of tissue associated with infectivity, and there is exclusion of the trace risk of contamination by such tissue.

The resulting remaining risk can be characterized as traces of traces of traces, which is a very low risk. This is a qualitative assessment, but this has been quantified, and that's exactly the numbers we have been shown yesterday by Dr. Bader.

I should point out that throughout Europe the spinal column is not normally removed from the food supply. Based on the current safety assessments of gelatin, we do not believe that such a step is necessary. Moreover, it cannot be accomplished except by a common legislation in Europe which is not in place and which is remote from us right now.

Therefore, guidance compliance, FDA guidance compliant material is currently produced out of bones coming from BSE free countries, a large part of it being the United States of America. Now whether there will be sufficient quantities of this bone to cope with the growing demand is yet to be found.

Now we are going into the process step which ensure, furthermore, the safety of gelatin.

The first step is the degreasing. Bones are subjected to an exhaustive washing and degreasing process, and these steps remove soft tissues and all the central nervous system tissues, a large part of the central nervous system tissues such as the dorsal root ganglia, as was described before.

A study about this degreasing, and that's on the next slide, has been performed by the University of Goettingen. In this study they found that in standard degreasing bone, which is a natural raw material for gelatin, for bone gelatin, no central nervous system protein was detectable by either ELISA or immunoblot test. No central nervous system proteins detectable.

In order to be able to measure something and to ensure that they were able to find some marker proteins above the limit of detection, they subjected

a load of cooled bovine heads to the degreasing process. As I mentioned earlier, bovine heads are excluded from the gelatin raw material supply.

Therefore, this test represents a stress on the degreasing process that will never occur in practice. In this new test with a load of bovine heads, it was shown that 99 percent or 98 percent of the proteins of the central nervous system were removed by the degreasing operation.

The second step in the process is the acidulation and liming. Studies of the acid and lime treatments used in gelatin processing were done by the Inveresk Research Institute in Scotland. In these studies the ability of acid and lime to inactivate a scrapie agent was evaluated in mice.

The mouse adapted scrapie agent, ME7, was used as a model. Please put on the next chart.

So the ME7 agent was exposed to acid treatment, to alkaline treatment, to a condition of both acid plus alkaline, and to no treatment. The treated solution were then inoculated into mice with various level of dilution. I think this was explained yesterday by Dr. Brown.

This allowed to calculate inactivation factors based on clinical and selected pathological

assessment at 18 months past inoculation. Reports of these studies, including the calculation of reduction factor, have been provided to the FDA.

Results of the study are shown on the next slides. So these are the latest Inveresk study results. They show that acidulation, acid treatment brings one large safety factor, a 10 infective agent reduction. Liming brings a 2.11 to 2.33 hundreds inactivation factor, and the combination of both acid plus liming brings a 3 large reduction, a thousand inactivation factor.

Then after these treatments you have additional treatments which are sterilization, filtration, deionization, and a lot of washing steps. Sterilization has been described by studies by Dr. Taylor and Dr. Rohwer as having the potential inactivation. It is suggested that sterilization conditions could impart a reduction factor of about 10^{-2} to 10^{-3}.

Filtration also could bring an additional reduction of infectivity. The ionization in some cases have been proven to bring a 10^{-5} factor, 100,000 inactivation factor. However, in order to be on the safe side, we allocate to these three steps of the process only a 10^{-1} factor, because these three steps

have not been validated exactly in the conditions of the gelatin production process.

If we take the 10^{-2} which was given by the degreasing steps, they're hundreds. If we take the 10^{-3} which was given by the Inveresk study, 1,000, and the 10^{-1} that we allocated from the other steps, we altogether come to a million reduction factor, 10^{-6}.

In the calculation which was shown yesterday by Dr. Bader, the inactivation factor which was taken in account was 10^{-3}, 1,000. Here we show a million in the safety assessment. In order to be conservative again, a factor of 1,000 was taken.

In conclusion, I would like to stress that our industry is constantly striving for additional safety. We will pursue any measure that can reasonably be implemented to improve safety.

Based on the information available at this time and the former safety assessment shows, gelatin from Europe poses no realistic risk as currently manufactured; that is to say, without removal of spines.

We believe that this committee, the FDA and the public can be confident in the safety of gelatin. This will be, obviously, further assessed in the meeting of June 5 at the University of Maryland.

GME's research program continues in order to evaluate a contribution to safety of the gelatin manufacturing process. I would like now to introduce Reinhard Schrieber who will discuss the next study that we are undertaking. I thank you for your attention.

MR. SCHRIEBER: Mr. Chairman, ladies and gentlemen, I'm Reinhard Schrieber, Executive Director of DGF Stoess in Germany. I'm also Director of Kinder Knox, the leading bone gelatin manufacturer in the U.S., and I'm the Chairman of the Regulatory and BSE Committee of GME in Europe.

When I presented one year ago to this committee the safety standards of gelatin made from European raw material, it was explained that this safety is a result of many different factors, one of which is a potential of the manufacturing process to remove and/or inactivate BSE infectivity which might have entered undetected the supply chain.

This has been noted by the risk assessment presented yesterday by Mr. Bader and just recently by Mr. Salmona as well.

Of course, the importance of the process ability to remove and/or destroy infectivity depends on the level of risk by this kind of contamination.

Nevertheless, the higher the process power will be, the higher will be the degree of additional safety margin achieved.

Therefore, it is in everybody's interest to know and to verify the ability of the entire gelatin process under the most realistic conditions. This has been as well one recommendation given by this committee to the gelatin manufacturers, and this has been taken up by us.

I will explain to you now what has been done so far and what will be our next steps. Again, when talking about removal and/or inactivation, I have to stress which of the production steps are most important in this respect.

There are no conditions known -- and we have heard this in these days -- which have the power to completely inactivate any thinkable level of BSE infectivity in just one step. Therefore, the cumulative effect of several processing steps with partial inactivation and removal power is very important.

To confirm this cumulative effect of these steps, this will be one of the goals of our new study. The first three steps, degreasing as a treatment, alkaline treatment, have been tested so far by

previous studies we just heard about.

In the filtration step, the filtered media used like diatomaceous earth and/or cellulose will most likely absorb parts of the infective agent during filtration of the gelatin solution. Regarding ion exchange, other non-gelatin studies have shown absorptions of infectivity of the resins used.

Many conditions of sterilizations have been studied in detail, but not the effect of the ultra high temperature treatment used by the milk and by the gelatin industry. So some correlation, just what we heard, is known, but the exact inactivation power has to be defined by our studies.

This sterilization is a sterilization of a watery solution under pressure. So it's not high temperature under dry conditions. It is sterilization of a solution.

Next slide. So what validation work has conducted so far. I'm just going very fast through this. The degreasing process is of special importance, because it cleans the outside of the crushed bones very intensively from soft tissue that could be infective.

For those members of the committee which have not been present last year, when I'm talking

about crushed bones, I'm talking about pieces of the size of your fingernail, because this is a first step. You are crushing the bones and then we are going -- this is crushed particles -- in the degreasing process. So this means for us inside will become outside after crushing, but we are catching all surface of these crushed bones.

Due to the difficulty, to test bones directly on infectivity in a bioassay by intercerebral injection and in the right test on the presence of those tissues to which infectivity is bound has been carried, and these are the results. I'm not going to repeat this, because this was just mentioned.

The sensitivity of the immunoblot -- and this has to be said as well -- or the ELISA test used in this study are not high enough to guaranty the complete absence of infectivity if no marker proteins are found, because that's a different levels of sensitivity of these tests; but the study design gives a good indication on the purification effect of the degreasing process, which was the goal of that study.

So we made an extra test to quantify this purification, and these numbers have been shown. Next slide, please.

To verify the effect of the SEN or alkali

treatment, we used in the old study the typical design of most studies published in the literature. So this means the infective agent, scrapie infected mouse brains, were placed for the designated time in the reactive agent, and afterwards tested on remaining infectivity in a bioassay. Ninety-nine percent of all studies published has been done in this way.

The results again are shown here. We reduced infectivity tenfold by acid, hundredfold by lime, and this reduction is cumulative. So the combined treatment, the acid followed by lime, gives a thousandfold reduction.

Next slide, please. One of the goals of our new study, of course, will be to confirm these effects done in the past with scrapie agent, now with BSE the agent at this time.

The protocol for the new study was developed with input from Dr. Taylor, one of the speakers here, from discussions with Dr. Rohwer, one of the leading U.S. experts who presented here as well last year, and with meetings with Professor Dormont, another well known French expert in TSE studies.

Despite the fact that normally the scrapie results are representative for BSE infectivity, too, the mouse adapted BSE strain will be used for spiking

the bones this time. This gives us further the advantage of less than one year incubation post inoculation instead of 18 months with mouse adapted scrapie. So we are somewhat faster.

The bone gelatin manufacturing process in use as a whole will be validated, but those unit operations not specifically tested yet will be included in a separate arm of the study, too. I will come to this.

By using a scaled down laboratory version of our process of specially built equipment for this study, it will be representative for the typical technical process used by the gelatin industry. Next slide, please.

What are the study parameters? A realistic worst case infectivity level of a raw bone mix would be too low to start with. So this infectivity level of what could happen in reality, we can't use.

So we have to choose an artificial high BSE challenge, and the challenge we had chosen is between 100 to 1,000 times higher than what it would be if all animals used were infected, older than three years with no spinal cord and dorsal root ganglia removed. So this is the challenge of our spiking.

Looking back to reality, because this is not reality, the spiking infectivity level is approximately 100,000 times higher than what can normally happen as long as in a country BSE is not epidemic, because in those cases, if it's not epidemic, here and there just one animal puts you up being infected, if not detected.

Next slide, please. So this means the highly infected mouse adapted BSE strain with a spiking level, just to give you the number, between 10^6 and 10^7 pair gram bones will be used. Our new study will demonstrate the effectiveness of the reducing power of the process, and will confirm the size of the safety margin against the realistic worst case scenario.

So what are we doing? The study will have three arms, the complete alkaline bone gelatin manufacturing process, the complete acid bone gelatin manufacturing process, and the separate validation of the different types and steps not tested yet.

So in reality, fresh, crushed and un-defatted bones will be spiked on the surface with a brain homogenate, which will then be dried on the surface to make removal during the degreasing process, which is following then, extremely difficult.

Then it will be run through the process as a treatment, alkaline treatment extraction. Then during this validation study of the complete process gelatins both directly after extraction and after further purification will be tested in a bioassay on detectable remaining infectivity.

The same is going to happen with the bones. Only difference is that there is no alkaline treatment here. Again spiking, testing after extraction, and testing after final purification.

The unit operations will be carried out by spiking an industrial gelatin solution with a brain homogenate at the level as if the previous operations -- these ones here -- would have no effect on the infectivity added. So this means we are spiking like with beginning, to start with a very high spike.

So what is the current status of these studies? So the preparation work has been finalized. The lab scale equipment has been built and validated already as being representative to simulate the industrial process. So this has been tested already.s

Several meetings and discussions with experts have taken place, and agreement on the design of the study and the protocol has been achieved.

We have requested as well the

participation of Dr. Rohwer in the United States, because he is very experienced mainly in tests with heat treatment, but at this time it is our understanding that test material containing BSE infectivity may not be imported into the United States. Therefore, based on this current knowledge, all research work has to be carried out in European labs.

Next slide, please. So what is the time frame? The first part of this study, the alkaline bone manufacturing, is expected to start in June this year. During the liming period of this arm, the next part of the study, the acid bone gelatin process which is shorter in time, will be carried out.

The incubation time for those mice showing no signs of neurological disease will be 300 days post injection out. Their brains will be pathologically examined, and the complete results of all parts of this study are expected to be available by approximately October 1999.

As this study suggests, GME is continuing in research into gelatin safety in cooperation with the European authorities and the scientific community who are responsible for addressing the public health issues relating to BSE.

We requested an opportunity to be here today so that we could keep this committee and the FDA informed about our progress. We will continue to do so in future. We are confident in the safety of our product, and we hope that this committee will communicate to the FDA and to the public that our product can be used with confidence under the conditions it is produced today.

On behalf of GME, I thank you, and I would like just to hand over again to Mr. Bill Stringer representing the Coalition of Gelatin Capsule Manufacturers. Thank you.

MR. STRINGER: Thank you, Mr. Salmona.

My name is Bill Stringer. I'm the Vice President of Quality and Regulatory Affairs at R.P. Scherer, North America. I'm here today representing the Coalition of Gelatin Capsule Manufacturers. Our coalition consists of members from R.P. Scherer, Capsugel and Banner Pharma Caps, and it represents the majority of the capsules produced in the United States.

The capsule industry consists of both hard gelatin capsules which are manufactured at one location and subsequently filled at separate locations, as well as soft gelatin capsules which are

formed, filled and sealed in one continuous operation. Gelatin is a key component of both types of capsules.

In light of the emergence of the possible BSE transmission to humans, we agree that there is a need for FDA guidance to address industry sourcing and utilization practices in FDA regulated products containing gelatin. Gelatin is used in a variety of products ranging from life saving drugs and injectable products to dietary supplements and foods.

As the new drugs coming out of today's pharmaceutical research laboratories are becoming more and more challenging to formulate into dosage forms which provide adequate bioavailability, capsule products are in many circumstances becoming the only optimal way to provide efficacious products. Also, many important dietary supplements, such as Vitamin E, are traditionally delivered in capsule form.

One fact seems to have gotten lost during the tumultuous times associated with the BSE crisis, and that is that gelatin has been used safely for years, centuries. The World Health Organization and various regulatory bodies have purported the safety of gelatin in the past, and it was actually echoed at the first TSE Advisory Committee meeting one year ago.

Additionally, various risk assessments,

including the PhRMA model, have provided quantitative data which supports the safety of gelatin.

Historically, the Coalition has attempted to work cooperatively with FDA on multiple occasions since 1993 to discuss issues and concerns relative to BSE. Likewise, we maintain regular open communication channels with the gelatin manufacturers and their trade organizations.

Most recently, we met with FDA officials immediately after the agency issued its industry guidance for the sourcing and processing of gelatin to reduce the risk posed by BSE in FDA regulated products for human use. At that time, we expressed concerns over a number of technical aspects associated with the first version of that document.

I'm pleased to say that the agency responded and clarified its position on certain topics, such as the uses of bovine hide gelatin and the ability to process appropriate starting materials into gelatin anywhere rather than specifically in the United States, and we would like to take this opportunity to applaud the agency's action in addressing these practical concerns.

The capsule industry utilizes different kinds of gelatin derived from porcine and bovine

sources. That derived from bovine bones is of primary concern from a BSE standpoint. Bovine bone gelatin is essential for the production of pharmaceutical capsule products.

Various technical aspects of gelatin, including its viscoelastic properties as well as certain chemical attributes, prevent capsule manufacturers from always being able to switch between different gelatin types. Porcine gelatin, for example, is not substitutable with bovine derived gelatin in every instance.

Bovine bone gelatin has predominantly -- is predominantly produced in Europe where there are eight plants currently manufacturing. The United States has not been a major producer of bovine bone gelatin with only two manufacturing sites.

Because of this, it is not surprising that the United States capsule industry has primarily utilized European sourced product for its bone gelatin requirements. Because of the reliance on European based bone gelatin and the insufficient supply of U.S. based starting material, the implementation of FDA's guidance on gelatin sourcing and processing caused the capsule industry grave concerns.

Let's review for a moment the situation

that existed one year ago. The gelatin exemption was in place at that time, which allowed the freedom to use gelatin derived from BSE countries in all FDA regulated products. In spite of the lack of limitations, however, the industry took its own steps to increase the safety of our products.

These steps included working with the gelatin manufacturers to ensure bovine heads were excluded from the supply chain in gelatin sourced from Europe, as well as instituting a moratorium on gelatin sourced from starting materials originating in the UK.

The TSE Advisory Committee's first meeting occurred in April 1997, and the committee took the view that there was not sufficient scientific evidence to support the gelatin exemption. The discussions during that meeting focused on narrowing the broad scope of the gelatin exemption based on good science and the need for risk assessment.

After the Advisory Committee's first meeting, the Coalition immediately developed a working relationship with Dr. Fred Bader who, as you know, pioneered the PhRMA peer reviewed risk assessment model for estimating potential risk from BSE transmission.

It is clear that more information is

needed about the removal of potentially infectious material during the extreme processing conditions associated with the gelatin manufacturing process. And as we've heard today already, much additional research is underway.

We would like to point out, however, that there is no evidence that gelatin or gelatin products serve as a vector for BSE transmission. Indeed, the probability that such an event could occur is extraordinarily remote.

Nothing is absolute, and there can never be a guaranty of absolute safety. As the FDA reviews new drugs and food additives, it constantly has to balance the benefits, such as that afforded by a multitude of capsule products, against the possible risks. Risk assessment is an accepted scientific methodology and is designed to provide a basis for determining that balance.

After the FDA issued its guidance on gelatin sourcing, the capsule industry faced significant challenges to comply. Coalition member companies, in concert with the gelatin industry, undertook a variety of very costly changes in sourcing practices and gelatin utilization strategies to begin the process of producing products consistent with the

procedures recommended in the FDA guidance.

These changes largely involved a shift in origination of bovine bone starting materials from Europe, as previously described, to non-BSE countries like the U.S. Again, given the reliance on European bone gelatin, this was and remains no easy task.

While we've made great strides in adapting to the guidance, the pressures in the supply chain are enormous due to the limitation of compliant starting materials. Incorporating any further restrictions such as those that you will vote on today in the form of prohibiting additional starting materials will have a major impact on the ability of the capsule industry to delivery valuable products to the consumers in the United States, and I cannot overemphasize that fact.

The resolution of certain technical issues would make the dilemma of adjusting to the guidance more reasonable, as we meet the pharmaceutical industry's need to produce life saving drugs with no significant impact on the safety of our products.

We would like to take this opportunity to briefly explain our position on the guidance itself, and we hope that the TSE Advisory Committee will take our position and practical limitations into consideration as you deliberate the questions before

you today.

It is important to point out that the guidance stipulates bovine spine must be removed when the starting material used to produce bone gelatin originates in a BSE country. There are two reasons why this statement severely limits the use of bone gelatin derived from starting materials originating in Europe.

First, there can be no guaranty that bovine bone originating from BSE countries can be excluded from the European supply chain, and this is through no fault of the gelatin manufacturers, due to circumstances beyond their control involving free trade between BSE and non-BSE countries in Europe. And I take you back to that supply chain chart that I showed you in the beginning.

Second, spine is not removed from starting materials anywhere in Europe on a commercial scale. While we are doing everything possible to comply, the availability of starting materials consistent with the recommendations in the FDA guidance is severely limited.

The industry, therefore, is faced with an impossible situation, trying to meet the needs of the growing capsule market involving new life saving drugs

such as protease inhibitors, while trying to procure gelatin consistent with the FDA guidance.

We believe that modification to the FDA guidance is appropriate, based on good science and risk assessment methodology, and we would like to describe our proposal for modification at this time.

First --

CHAIRMAN BROWN: You're going to have to wrap this up very quickly.

MR. STRINGER: We call attention to the fact that there is not a significant difference in risk between bovine bone gelatin source from U.S. starting materials where the brain and spinal cord have been removed compared to similarly processed starting materials originating in Europe, excluding the UK, as I previously described. Both scenarios represent insignificant risk.

We would also like to reiterate that the specified risk materials, brain, skull and spinal cord, are removed in Europe by law in those countries reporting native cases of BSE, as we've already heard. The removal of specified risk materials in BSE countries in Europe represents a significant advancement over the situation that existed when the broad gelatin exemption was in place one year ago.

This substantial improvement in industry practice has significantly improved the safety of European based bone starting materials. The additional requirement relating to the use of spines is, therefore, unnecessary.

We request, therefore, that the requirement relating to the limitation on the use of spine be deleted from the guidance.

In closing, I'd like to reiterate the fact that gelatin is a safe product. It's been used safely for human consumption for centuries, and while we would all like to have additional scientific information in decision making, it would be incorrect to focus solely on the need for additional information and ignore what we know about the safety of gelatin.

We believe strongly that good science mandates the application of quantitative risk assessment principles in order to make the transition from theoretical perceived concerns to practical application of regulatory policy.

Thank you.

CHAIRMAN BROWN: I think we will adjourn for lunch, unless there is a burning question from the committee. We're running about 15 minutes late, and I would hope that everyone could be back, because I

expect to start the afternoon session as scheduled at two o'clock.

(Whereupon, the foregoing matter went off the record at 1:14 p.m.)

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AFTERNOON SESSION

Time: 2:02 p.m.

DR. FREAS: If you would take your seats, please, we're about ready to get started. While people are sitting down, if the committee members would make sure that they receive at the bottom of their stack three handouts on the dura mater, and also anybody who does not have David Asher's questions, I have extras up here, and I'll pass them out.

CHAIRMAN BROWN: Continuing our discussions on gelatin, we have a final presentation by Dave Taylor about regulatory policies in the European Union on gelatin, and that will be followed by the charge to the committee by Carol Vincent, at which time we will begin our deliberations.

If we can get through those deliberations in a timely way, we will have an extra few minutes and consider what was overlooked by me earlier today, which was the question of glycerin.

David?

DR. TAYLOR: Thank you, Paul.

I've been asked to try to outline for you the current European Commission position on gelatin. Questions regarding the safety of gelatin have been discussed from time to time. The EC Scientific

Veterinary Committee in '94 regarded it as basically safe, regardless of the nature of usage, and at that time, I think, almost without any regard to sourcing implications.

The Scientific Committee on Food in Brussels in '96 recognized the concerns arising from the potential transmissibility of BSE to humans, and reckoned that gelatin should only be produced from raw materials coming from areas where BSE does not occur in epidemic form.

Some degree of reservation was also expressed in '96 by CPMP and the EC's multi-disciplinary scientific committee, which as you probably realize has spawned a number of working groups. I've already referred to the one which considered tallow.

The working group which was established in 1997 to look at the problem relating to gelatin has now reported to the Scientific Steering Committee, who in turn have produced an opinion on the subject.

The question they set out to answer was: Can gelatin, as it is produced currently, be considered to be free from BSE infectivity and, if not, under what sort of conditions can it be considered to be safe?

As I said before with regard to tallow, one of the problems of interpretation of the SSC opinion is that some of it depends on opinions of the -- Sorry, I'm talking about the wrong slide here. Okay, we'll just take them as they come.

The newer data on tissue infectivity which Ray Bradley has discussed with you have been considered by the Scientific Steering Committee. In view of the presence of infectivity in the dorsal root ganglia which, at least in bovines, cannot really be readily separated from the spinal column except by relatively tricky surgery, the -- well, the thought is that this would necessitate removal of the whole vertebral column.

As far as bone marrow is concerned, Ray Bradley has also shown you why this at the moment is a result which cannot be interpreted. In the fullness of time, we may be able to say a bit more about bone marrow if the other groups in the progression of samples that he described actually become positive. If they don't, there may be a question mark hanging over bone marrow or the balance of opinion may be that this single result was a spurious result.

If the result is confirmed, then the opinion would be that bones from older animals -- for

example, over 30 months -- might need to be excluded. I say at the bottom, the bone marrow result is uninterpretable, because it was from a single group of mice of which only a few were affected.

The actual SSE opinion regarding manufacture of gelatin from -- Sorry, this is the one I thought was -- I showed this slide earlier with regard to tallow, because the problem of interpreting the current SSC opinion is that they make certain comments about the status of different countries with regard to their risk or presence of BSE, and at the moment they haven't decided how they are going to categorize groups 2 and 3 there.

Also, as I explained, what will finally be in the full shopping list for SRM is not yet -- has not yet been decided, and I won't go into these points here, because I mentioned them earlier on.

In terms of the actual gelatin, the EC committee opinion is that, if this is for use in -- If it's for human consumption or for use in cosmetics, prepared from materials obtained from high risk countries, then no bovine bones should be permitted generally, but exceptions may be made on the basis of the origin and age of the donor animals.

Ray Bradley discussed with you how they

argued that it could be perfectly acceptable to use bones from animals under the age of 30 months.

Bovine hides are permitted, if they are from carcasses fit for human consumption, and pig material is okay universally, providing it's fit for human consumption and the carcasses have been gone through dedicated lines. In other words, you're not mixing pig and bovine abattoir production.

From the lower risk countries, they say that bovine material should be fit for human consumption, but that SRMs should be removed.

Where the materials are from BSE free areas or areas considered to have a negligible risk from the disease, there's no restriction except that the bovine material should be derived from carcasses declared fit for human consumption by ante and post mortem investigation.

As I said this morning with regard to tallow, the problem with countries with unknown TSE status is a bit difficult, because they are suggesting that you conduct a risk assessment. My own feeling is, if the status of a country is currently unknown, you are probably going to be forced into this direction here; in other words, regard it as high risk in the absence of solid information.

Whether gelatin will be used as a reagent and ophthalmological products or in vaccines, they suggest using special grade tallow, which I'll explain on the next slide.

If it's for industrial use such as photographic and other technical applications, they say manufacture by an appropriate process without, as far as I could see, defining what appropriate means.

There should be some warning sign on the label for these products that you should avoid direct contact with them in the workplace.

Finally, they say that if direct contact or ingestion is likely to occur, then you apply the restrictions relating to the manufacture for human consumption. By that, I mean, you assess things by the risk relating to geographical area.

Finally, for pharmaceutical and parenteral use, without uses for oral or topical use but not ophthalmic, restrictions should apply that have already been considered to be appropriate with regard to production for food and cosmetic use.

Consider the use of special grade gelatin for application of products to large areas of damaged skin or open wounds. by special grade, they mean apply the geographical criteria that apply to raw

materials which we described for gelatin fit for human consumption, plus appropriate purification procedures.

Again, I don't think -- There's no interpretation of what is meant by appropriate purification procedures.

Then for the parenterals, the ophthalmics, excipients and implantable devices, they also say consider the use. Doesn't suggest it's demanding that, but says consider the use of special grade gelatin; and as one would always do, I think, consider the benefit to risk ratio.

Once again, I suspect that manufacturers here have probably looked at these regulations in more detail than I have, and I'd be happy to hear if I'm making any fundamental errors. Thank you very much.

CHAIRMAN BROWN: Thank you, David. Any questions for David on these European regulations?

If not, we'll go directly to our charge by Carol Vincent. Carol, if you would just stay there for just a second, Bill Freas reminded me that, although we think there is not, we would be remiss in not at least asking whether there are any questions that would have been asked during what we didn't have, which was an open public hearing on the issue of gelatin, just questions or comments with respect to

gelatin.

For the record, there were none. Go ahead, Carol.

MS. VINCENT: Thank you, Dr. Brown. So what do we know and what do we not know, and what are our regulatory concerns at this point?

A few things we do know now. I'll remind you, research findings published October 24, 1996, provided strong evidence of identity between the agents of BSE isolated from cattle and the agents isolated from several NV CJD patients.

Also on December 1, 1997, the SEAC public meeting, part of their report included the committee review of the results of long term pathogenic experiments, which we've heard quite a bit about these two days, relating to dorsal root ganglia and provisions results on bone marrow, and has provided advice to the government on this matter.

This was issued on 3 December and resulted in British legislation prohibiting the sale of beef on the bone at the retail level.

We all know that the geographic occurrence of BSE in native animals appears to be spreading or continuing to spread. USDA published an interim rule and request for comment on January 6, 1998. This is

the one Dr. Detwiler referred to earlier as effective retroactively to December 12, in accordance with the date of the APHIS memorandum.

It places essentially all of continental Europe on the list of countries where BSE has been identified or where there is a high likelihood it could occur.

Over these two days we've heard several pieces of newer data on the distribution of the BSE agent in infected cattle and experimental animals, and the results of inactivation studies provided by the gelatin industry.

One year ago at the charter meeting of this committee we discussed the types of agent clearance validation protocols that we microbiologists review for animal derived products in the New Drug Applications at the Center for Drug Evaluation and Research. I'm repeating several of these overheads from last year. I think they need to be repeated again.

This is the citation for the sterilization process validation guideline. It's been in several fora. It went in the Federal Register on December 3, 1993, at 58 FR 63996. It was also published in November of '94 as a guidance, and it's available on

the FDA's home page at the CDER Web site under the guidance documents. I don't have the URL.

I cite this specifically because a paragraph in there is a very good justification and expectations in the validation protocols.

Some of these -- Okay, excuse me. We pointed out, as clearly explained in the sterilization process validation guideline for sterile drug products admitted -- submitted to CDER and CVM, that the validation protocol should follow as closely as possible the specific manufacturing process for the subject drug product, and that laboratory pilot scales, substitution of a scrapie agent is acceptable.

These experiments -- they should be experiments that are designed to give you ample, valid, scientific proof that the particular procedure, whatever it is that you're doing, that you are validating the procedure and the efficacy of removing these agents, as demonstrated. You have a series of protocols and scientific experiments.

The object is to reproducibly deliver a product free of the specified infectious agent. That applies to any or every type of validation protocol for any purpose.

Experimental data and control procedures

allow conclusions to be drawn about the efficacy of the inactivation process. Obviously, we're concerned about inactivation in these inoculated studies with the gelatin process.

Your results and conclusions should determine that the clearance is validated, procedures and conditions are fully representative and descriptive of the manufacturing process. You should start at the beginning and finish at the end. You should not arbitrarily jump in and pick out two or three spots and not complete the entire manufacturing process, because that's not representative of what you do.

Next slide, please. Here is probably most of the same information, slightly rearranged. Pilot scale is okay. You want a consistent model system. You want predictable animal response. You want your inoculum to be under control or under limits. This means you should have enough experience in your animal system with this agent, enough time so that you can calculate 95 percent confidence intervals for it.

So somewhere from ten, 20, 100 times, and you need to work out the dilution for your system that works to give you very reproducible results time to time. Once again in bold, follow the manufacturing

procedure. Don't substitute steps. Don't omit steps. Don't add steps in the validation protocol.

Sample any of the steps that would have an effect on your inoculated agent. Follow your same time frames. You want to design your assay for a reproducible endpoint. Referring back to experience with the agent, you want to bracket your ID_{50} for the inoculum -- I'm sorry, LD. You want to bracket your LD_{50} for your inactivations. It means you want to have a balance. You want to have endpoints and positive controls positive, negative controls negative.

We noted at that time that we wanted to see follow-through on the spiking and sampling process. For example, if the manufacturing process includes several steps purported to inactivate a TSE agent and if the agent is inoculated at these same steps, we need to see the infectivity reduction factors not only following each step but also the cumulative effect of all manufacturing procedures taken together with the result in the final product.

While we agree that some inactivation may occur with the discrete steps, they may not be cumulative, and they may not follow first order kinetics, and the slope of the inactivation curve may

not be linear. This is what happened with polio vaccine in 1955.

This is the title of a talk by Melnick at the BSE meeting in London in 1990. The reason I'm putting in this mention of the Cutter incident is because I think it's one of the best examples in the literature of a biological phenomenon not following a mathematical model, and the danger of assumptions.

We know from various inactivation experiments by several researchers that there are resistant subfractions of the TSE agents surviving the initial sharp decrease in infectivity.

One of the better known examples of a similar pattern of inactivation by chemical agents in classical virology is the inactivation curve which resulted in the asymptotic region. This is referred to and is widely understood to be responsible for the Cutter incident where certain logs of formaldehyde inactivated polio vaccine were released in April 1955.

Approximately 4 million doses of polio vaccine were distributed. Shortly thereafter, 204 cases of paralytic polio with 11 deaths occurred. Seventy-nine cases were vaccinees with an incubation period of four to 14 days. 105 cases were family contacts of the vaccinees with incubation periods of

eight to 28 days, reflecting the double incubation time, and the 20 other cases were community contacts.

The relevance of this example is -- This example is relevant to other infectious diseases, including the TSEs where amplification and multiplication of the infecting agent are part of the pathogenic mechanism, regardless of the identity of the infecting organism.

Recent information provided to the FDA by the gelatin industry indicates the acid and lime processing may inactivate from one to two logs of the inoculated scrapie agent, respectively. Twenty, 45 and 60 day reduction factors in lime were in the 2 log range, and there does not appear to be an increase at inactivation over time; and reduction factors derived from the separate treatments of acid and lime did not appear to be additive.

In an additional combined study, the acid treatment was followed by neutralization, and then 45 days of lime treatment provided a reduction factor of 2.87 logs. That's about 740 full reduction.

In the context of an infectious disease, it depends upon multiplication and amplification of an etiological agent as part of the pathogenic mechanism. A manufacturing method which affords several

hundredfold reduction of an infectious agent would not ordinarily be considered adequate.

These are some of the facts we know. There are other validated we do not know or haven't received yet, and there continue to be issues that we regulatory agencies are concerned about. These issues will be further discussed at length at Dr. Hueston's workshop June 8 and 9 in College Park with Dr. Hellman. Don't forget your registration materials.

At this workshop we hope to develop guiding principles that may have concrete relevance in the decision making process for regulatory agencies and manufacturers.

Now we repeat the charge and questions to the committee, as stated earlier by Dr. Asher:

To consider whether the safeguards recommended in the most recent FDA guidance document are appropriate and adequate to protect the public from exposure to the BSE agent in gelatin for oral consumption or for topical application when the gelatin was prepared from bones and hides of -- should be bovines; now you know I got my slide from David -- born or residing in the BSE countries or bovines from BSE status unknown countries.

Next, question 1: Concerning the safety

of bovine bone gelatin, can healthy cattle from BSE countries or from BSE status unknown countries be considered a safe source of bones to produce gelatin intended for oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE free herds, and the heads, spines and spinal cords are removed from carcasses immediately after slaughter?

Number two: Can healthy cattle from BSE countries or from BSE status unknown countries be considered a safe source of hides to produce gelatin intended for oral consumption by humans or for topical application to humans if, as previously recommended, the cattle are from BSE free herds, and contamination of the hides with the CNS tissues and eyes is avoided?

Thank you.

CHAIRMAN BROWN: Thank you, Carol. Let's tackle question first. For the speakers this morning? Yes, okay. Sure.

DR. OLANDER: To the gelatin, what are your critical control points, and how do you do your testing in your HACCP procedures?

MR. SALMONA: Okay. We have the traceability, which has one critical counterpoint, which is collated.

DR. OLANDER: The what?

MR. SALMONA: The traceability, which is audited permanently, and then we have several steps in the process. All the steps which were shown in the validation studies belong to this control point, which is liming time, liming acidulation time, the degreasing parameters, etcetera, etcetera. All the parameters that we have shown this morning belong to the HACCP parameters that we monitor.

DR. OLANDER: Okay. No, I'm not done. With respect to the removal of heads from, how is that checked? Is that done at the slaughter plant or are you checking? Are you checking your materials when they come in?

MR. SALMONA: It's done as upstream as possible, which means that we have in place to our supplier of raw material not to deliver heads. Okay? In some countries -- In a country with BSE, the problem is already taken care of, because the slaughter house have to discard their heads. Very simple.

In other countries, heads are discarded by the collector, and then there is one further check when the trucks of bones arrive to the degreasing plant, and then we sort out things which shouldn't be

there; and if there is one head, it's sorted out, but this happens extremely seldom.

DR. DETWILER: I have a question for any of the gelatin manufacturers. I can appreciate that you said the amounts -- you can't get enough -- okay? -- and if you imported bones from the United States over to Europe to process, I can appreciate that.

How about even sourcing from other countries that have done, you know, risk assessments and surveillance over the past eight, nine years, such as Canada, Argentina, Australia, New Zealand? How about sourcing raw material from those type of countries?

MR. SALMONA: As of today, there are very limited quantities available from these countries.

DR. DETWILER: I mean, that's available to bring in, but there are not shortage of bone, I would think. Right?

MR. SALMONA: Yes, but they are not transforming to gelatin bones, and this is not happening right now. It will take some time before this can be developed.

CHAIRMAN BROWN: Ray?

DR. ROOS: I have a question for perhaps the gelatin manufacturers, but also maybe to UK, and

it has to do with what, I guess, underlies one of the issues here, which is removal of the spine.

I have a feeling that the manufacturers thought that this was a difficult task to carry out, whereas, as I see it, the UK is going to have this as a routine procedure. I just wondered whether we could hear a little bit more about how difficult this is to be accomplished.

CHAIRMAN BROWN: First to Ray. Is the removal of the vertebral column, including the spinal cord, going to be -- or is now a standard procedure?

DR. BRADLEY: Well, spinal cord has been for some period of time, in fact since 1989.

CHAIRMAN BROWN: How do they get that out? They pull it or do they slice the spine?

DR. BRADLEY: No. They cut it --

CHAIRMAN BROWN: They cut the cord?

DR. BRADLEY: They pull and cut, and then they scrape with a special tool down the spinal canal to remove as much of the fatty tissue that's present, so that the cord canal is absolutely clean.

CHAIRMAN BROWN: But the vertebral column is also cut? That is, the column is sawed?

DR. BRADLEY: Each carcass is sawn in half as part of the procedure in the abattoirs. That's not

true in all countries for processing beef carcasses.

CHAIRMAN BROWN: So the carcass is split in two with a saw?

DR. BRADLEY: Yes.

CHAIRMAN BROWN: Leaving open the spinal cord in its container, which is the vertebral column?

DR. BRADLEY: Exactly. In the perfect situation, the canal is split exactly in the middle. This is done by very skilled operators, and they're very good at doing it.

The spinal cord can be left in one piece, but it can also be cut through perhaps once or even twice in the course of his vertical cut, depending partly on skill and partly on the curvature of the spine, which sometimes naturally occurs in cattle.

So the spinal cord has been out since 1989.

CHAIRMAN BROWN: If the operator is not as skilled as he might be, and cuts to the side --

DR. BRADLEY: Yes.

CHAIRMAN BROWN: -- any such cut would potentially contaminate that particular carcass. I'm sure the saw blade isn't changed between carcasses.

DR. BRADLEY: This might have happened in the earlier days, but it doesn't happen now, because

since April 1995 we've had the Meat Hygiene Service which is a service whose purpose is to ensure that each spinal cord is removed, even if the cut is off-center. That is actually checked in every individual case.

In order to see that the Meat Hygiene Service is doing its job, there are spot checks by unannounced visits by the state veterinary service to inspect carcasses to see that the cord has actually been removed. Since March 1996, as reported in the bulletin, namely since the onset of new-variant CJD, not a single spinal cord has been found or any portion of a spinal cord in any carcass in Great Britain.

CHAIRMAN BROWN: This is done manually? It's not like running a steer through a circular saw?

DR. BRADLEY: No, no. It's done individually by --

CHAIRMAN BROWN: Well, you know, veterinary -- Slaughter houses are gross places anyway. So okay. Yes?

DR. BRADLEY: Now your second question was about the spinal column.

CHAIRMAN BROWN: Yes.

DR. BRADLEY: Well, since March, again, 1996, at the announcement, all meat has now been

deboned. So, actually, if you want to sell sirloin or what would have been a rib steak, you've got to actually take the meat from the bone. So it's physically got to be done in every single carcass, and not only from British cattle but from imported cattle as well, which aids, of course, audit for this.

CHAIRMAN BROWN: So the second part of the question is -- the crux of the question, Ray, I guess, in part was what's the big deal about getting the vertebral column out if you're going to split the carcass in half anyway?

DR. HUESTON: So just to follow up, so that means the canal is removed? The column? Is that what you said? You said all the meat is removed from the bone.

DR. BRADLEY: No. What happens first is in the abattoir when the animal is killed and guts are removed and so on, it is at that -- during that process that the carcass is sawn in half and the spinal cord is removed. Then the side of beef, having been inspected with spinal cord absent, goes to a meat cutting plant where the meat is actually removed.

That could be on the premises in a separate part of the premises or it could be at another site, and then the meat is physically removed

from the bone.

Now before the rule that all meat had to be deboned before sold to the consumer, 95 percent was deboned anyway, you know, but not necessarily in a licensed cutting plant. It could have been done by the local butcher. Now it has to be done in a licensed plant, and inspection supervision.

DR. HUESTON: So is that spinal column part of the bone material that's used for gelatin?

DR. BRADLEY: No, because we're not allowed to manufacture gelatin or tallow from either skulls which are, in any case, specified risk material, or from vertebral column, which is not strictly specified risk material, but is not allowed to go into gelatin manufacture or tallow manufacture and, of course, cannot get onto people's dinner plates either.

CHAIRMAN BROWN: This is in the UK?

DR. BRADLEY: That's in the UK.

DR. HUESTON: So, Paul, the committee recommended that the brain, spinal cord and the spine--

CHAIRMAN BROWN: Head, spines and spinal cords.

DR. HUESTON: I just want to make sure I

understand why we made that recommendation.

CHAIRMAN BROWN: That means the vertebral column and its contents plus the head.

DR. BRADLEY: If I can just add a little bit of substance to why the spinal cord should be removed, it's because of the inability to remove the dorsal root ganglia. That's the real -- Yes, the spinal column. I said cord. I meant column. The spinal cord, the bony skeleton, has to be removed.

The reason for that is because of the dorsal root ganglia.

DR. HUESTON: But are we actually risking contamination in the preparation of gelatin, having that dorsal root ganglia embedded rather firmly in the spinal column or was this in fact perhaps an unnecessary requirement in the gelatin preparation?

DR. BRADLEY: Well, the way it came about was from the Commission in regards to gelatin and tallow manufacture. In regard to human consumption of meat, it was one of the options provided to the Minister to decide as to how the security of public health could be provided.

When we had the information about dorsal root ganglia infectivity, the first point that the SEAC made was this must be made known to the public,

point ont. Then there were options.

Either you do nothing about it -- that's option one. Secondly, you debone all meat. That's option three. Then there was a halfway house, which was debone meat from animals over two years of age rather than the 30 months. The Minister chose actually the strictest option.

DR. HUESTON: If we get back to these sourcing of bones for gelatin --

CHAIRMAN BROWN: We've had an industry man here waiting to speak for a second.

MR. SCHRIEBER: I'd just like to make one further remark with regard to the continental Europe. These decisions in the UK are done based on the fact that in the UK BSE is epidemic. Because changing slaughtering procedures, which means removal of spine, is a tremendous load to the meat industry and that's what we have to keep in mind, so therefore, outside UK no government found it appropriate with regard to the BSE status in all these countries to implement this procedure, because that's what is necessary, because we can't do it.

It has to be done by the meat industry, and if the government thinks this is not necessary to safeguard human health, it's not implemented, and

that's a situation we are in.

We have to be careful to say everything which is fine in the UK is fine for the rest of Europe. With regard to the remaining part of Europe, what is the number of BSE cases. We have seen these numbers. They are very, very slow. So, therefore, the local governments have thought there is no additional measure necessary beyond what is already implemented.

CHAIRMAN BROWN: Yes. Mr. Schrieber, I agree with what you said. I would also say that it is not the business of this committee to take into consideration the impact of any of its recommendations on the industry. This is the task of the FDA.

Our task is to advise the industry -- not the industry, but the FDA based on scientific evidence on the advisability or inadvisability of something. It is the FDA that is making a policy. We are not, and our input is a scientific input that they blend with the kinds of considerations you brought up, but it is not the job of this committee to take those considerations under consideration.

Yes?

MR. SALMONA: Just one piece of information I'd like to add to make it clear. I

understand from what Mr. Bradley said that in the UK the removal of spine does not occur directly after slaughtering. It can occur much farther down the stream.

DR. BRADLEY: Yes.

MR. SALMONA: Okay. So even in the UK the procedure which is used right now is not the one which is recommended by the guidance in this current status.

CHAIRMAN BROWN: Just in terms of where the cord is taken out.

DR. BRADLEY: But the cord is taken out in the abattoir. The deboning takes place not in the abattoir but in the cutting plant.

DR. ROOS: Just to -- As I understand it, the spinal column and the rationale for removing the spinal column, as I see it, shouldn't affect the safety of gelatin in any way, unless I missed something.

CHAIRMAN BROWN: Well, except I think maybe we all are missing something. I assume that the vertebral column is disappearing simply because it is impossible to get dorsal root ganglia out of it and, therefore, that gets rid of a known infectious tissue. So it does bear on anything that is produced from it.

If it's not there, you lose your dorsal

root ganglia, and as you lose the dorsal root ganglia, that's a plus.

DR. ROOS: But if your starting material to make the gelatin doesn't include t he dorsal root ganglia --

CHAIRMAN BROWN: But it would have to, if they used the vertebral column.

DR. ROOS: But they don't.

DR. DETWILER: Only in the UK.

CHAIRMAN BROWN: Only in the UK.

DR. BRADLEY: Only in the UK.

CHAIRMAN BROWN: That's the whole point. In Europe the spinal -- the vertebral column is part of the mix. Okay? Everybody clear on that?

DR. ROOS: So in European countries the spinal column is part of the --

CHAIRMAN BROWN: Yes. Let's use the word vertebral column so there's no question about what's what.

DR. ROOS: Vertebral column is part of the raw material.

CHAIRMAN BROWN: That is correct.

DR. BRADLEY: Might I just add also that the bones that we dispose of, as it were, because we're not allowed to consume them -- they're not

regarded as specified risk materials in the same category as brains and spleens and so on. They are sort of intermediate category. You're just not allowed to consume them.

DR. ROOS: So, Paul, doesn't that mean that the vertebral column is removed, if it forms the raw material for gelatin in these countries?

CHAIRMAN BROWN: If it is removed?

DR. ROOS: Yes.

CHAIRMAN BROWN: That is, as we speak, it's being removed or do you refer to it should be removed?

DR. ROOS: Well, you're telling me that it's part of the raw material, the --

CHAIRMAN BROWN: As we speak, that is correct. Yes. It is now.

DR. ROOS: So, therefore, it must be removed by these countries?

CHAIRMAN BROWN: Well, that's one of the things. It's not.

DR. HUESTON: No, the current requirement -- the current FDA guidance --

CHAIRMAN BROWN: I don't understand the confusion, frankly, Ray.

DR. HUESTON: Well, can I try to bridge

the two of you? I believe Ray is saying that the current guidance states that it must be removed.

CHAIRMAN BROWN: Guidance, yes.

DR. HUESTON: Current guidance. And the gelatin manufacturers are suggesting that that is difficult to meet. So they're -- I believe that's what we're discussing.

DR. ROOS: But did I hear that they're using that as the raw material to prepare gelatin?

CHAIRMAN BROWN: Not the raw material, but it's going into it. Yes.

DR. ROOS: So then it must be being removed. Nevertheless, they say that it's difficult.

CHAIRMAN BROWN: No. What's going on?

DR. HONSTEAD: Paul, the whole -- When they take the meat off a carcass, the whole thing that's left is the bones -- It's skeleton, and that whole thing, if I'm not right, is being used to crush and make gelatin. So it's not being removed from human consumption. It's wanted to be removed from -- Okay.

CHAIRMAN BROWN: All right. Now we're all clear about that. Are there any -- Yes, Barbara?

DR. HARRELL: I think I have an inconsistency. Mr. Salmona said that there was

traceability. Is that not correct -- as far as the source? Then Mr. Stringer said that the current FDA restrictions do not improve the situation, because there is no traceability in Europe.

Then he came back with a statement saying that Europe and the U.S. source material were equal. I mean, those are contradictory statements. If there is no traceability, then -- you know, you said because of the free market system, there was no traceability.

So how could it be equal to the U.S. source material?

MR. STRINGER: The comment that it was equal to U.S. sourced material has to do with the risk assessment model. If you remember the chart that Dr. Bader put up yesterday, the material sourced from Europe where spinal column, vertebral column, has not been removed was still within the oval for gelatin insignificant risk that was presented.

Within that oval also is similarly processed material derived from U.S. starting material. So the point that I was making was, if you compare starting material that comes from the U.S. where vertebral column is not removed versus starting material from Europe, excluding the UK, where vertebral column is not removed, the risk according to

the risk assessment model is nearly equal, and they both represent insignificant risk.

CHAIRMAN BROWN: Yes, and this is one of the problems of using models, because the presumption there which we heard from Dr. Bader, which is a reasonable presumption but probably untrue, is that BSE exists in the U.S. at the rate of one per million. I think it's far more likely BSE doesn't exist in the United States.

So already, you've got one presumption that is a very open question, and throws the equality equation into serious doubt.

DR. LURIE: Can I make another comment on the risk? Yes? On the risk assessment, sort of alluded to a spokesperson from the FDA a moment ago, but the assumption in, I think, Dr. Bader's models, even though he didn't quite present it, and certainly in the model that gelatin manufacturers presented was that you could multiply together the probabilities or the fractional reductions in the likely load of the TSE agent by successive steps.

In fact, that really isn't a reasonable assumption at all. Most likely, if there were some infectious organisms that were to evade the first step, they would probably be more likely than average

to evade the second and then more likely on average to evade the third.

This isn't to say that they wouldn't eventually be reached, but the point is multiplying them together leads to an underestimate of the risk. It cannot lead to an overestimate, but only an underestimate.

Obviously, that's something for you to consider for your risk assessment, but it just really does undermine the 10^{-6} reduction that you suggested. Indeed, as was pointed out, there's not an additive effect of the separate steps in the Inveresk study. Having more is having less, but they are not additive.

CHAIRMAN BROWN: Yeah. I think that's exactly right, Peter, and in fact, if you look at the numbers, although you can argue that any given test within a half-log of each other would be different, the fact is that when you added up the separate steps and compared it with the combined acid step, the combined acid step actually was a half-log lower than the added step.

So it is, I think, absolutely true that games played with additive reductions often are deceptive. That is why in a good validation study or an ideal world you spike each step to see what the

clearance is per step, but you don't fail to do what the gelatin people are going to do now, which is to do the entire thing from start to finish and see how it matches up.

Are there other questions? Yes?

DR. HUESTON: Can I ask for a little clarification? There are two types of bone gelatin, if I understand correctly. One is the acid process alone, and the other is both the acid and alkaline. Can you help me draw the connection between those two different processes and the hard capsule gelatin that's of concern, the relative amounts going to each of those?

MR. STRINGER: There are two types of bone gelatin, as you pointed out, that derived from an acid process and that derived from an acid and liming process. Both are used to make capsules. That which is produced using only the acid process is by far and away a very small minority compared to the overall gelatin used to make capsules, for both hard and soft.

CHAIRMAN BROWN: Is there any use of it? Is there any gelatin produced from the process which uses only acid --

MR. STRINGER: Yes.

CHAIRMAN BROWN: -- which is not able to

be produced from the combined acid/liming procedure? In other words, is there any mandatory use of acid for some kind of gelatin as opposed to both acid and alkali?

MR. STRINGER: Only as far as the uses of those gelatins are concerned. So the industry -- the capsule industry would go to the gelatin industry and say we need only acid processed gelatin for this particular application, but --

CHAIRMAN BROWN: But if it were both acid and alkali, would it also be equally usable?

MR. STRINGER: In many cases the answer to that question is definitely, no.

CHAIRMAN BROWN: You would have to have just -- In other words, the gelatin process that included the alkali would preclude certain uses of the produced gelatin?

MR. STRINGER: Most definitely.

CHAIRMAN BROWN: Give me an example.

MR. STRINGER: There are certain viscoelastic properties that are different between acid processed gelatin and lime processed gelatin. In addition, there are chemical properties between the two types of gelatin, and in certain situations, while you could physically make the capsule, it might not be

stable under the conditions required in the New Drug Application.

So, therefore, using a lime processed gelatin might solve one problem but create a much larger one in terms of stability, dissolution, efficaciousness, bioavailability.

CHAIRMAN BROWN: Yes. I was just raising the possibility of a requirement that acid and alkali be used routinely, and that is not a practical way to get at the problem; because you need acid treated gelatin for some purposes.

MR. STRINGER: That is definitely correct.

CHAIRMAN BROWN: Okay. Yes, Linda?

DR. DETWILER: Don't go yet, please. Thank you.

What exactly must be done when you're sourcing bone gelatin? What's unique about obtaining the bones, I guess, that makes it difficult to go to other countries to source?

MR. STRINGER: Okay. Let's be clear on that, and I think it's a good question, because there was some confusion on it.

The guidance currently states right now that, if you source the starting material from a BSE country, then the spine, in addition to the short list

of SRM, must be removed.

In Europe it's impossible to achieve that, because the spine, as you've heard, is not removed. In those countries where there is native BSE, the brain and spinal cord is. The spinal cord is, but not the spine.

So what's happened is the capsule industry, prior to the issuance of the guidance and even now, is heavily reliant on European based gelatin, because it's insufficiently produced in the United States. There's not enough plants. There's not enough starting material.

So when we look at trying to procure gelatin made in a manner consistent with the FDA guidance and we go to our gelatin suppliers, there is insufficient supply.

So we are in a very tenuous situation in trying to produce products to the growing needs of the industry while at the same time trying to maintain procurement practices that are consistent with the guidance.

DR. DETWILER: That wasn't my question. My question was your source material, your raw material, the bone. What is unique about obtaining bone for bone gelatin that it would have to come from

France or Germany versus, you know, Canada or the United States, Argentina, Australia, New Zealand?

MR. STRINGER: Nothing. It's availability. It's simply a question of availability.

DR. DETWILER: So you're telling me that only Europe has enough cows versus Argentina, Australia, New Zealand.

MR. SCHRIEBER: The bones are there, but no manufacturing facilities to make bone chips from the bones; because no, let's say, company of the meat industry in Brazil or Argentina has ever started to make gelatin bones.

DR. DETWILER: See, that was my question. Okay.

MR. SCHRIEBER: The plants are not there.

DR. SCHONBERGER: What about shipping?

DR. LURIE: Can you speak -- I think somebody said that there were two plants in this country and eight in Europe. Can you give us a sense of the actual production used by American gelatin manufacturers?

MR. SCHRIEBER: Yes, we can. We can show you the relationship between imported and domestically used. Yes. We have it.

CHAIRMAN BROWN: I just want to say we

don't want to get too far afield on this, because this again is totally commercial; but go ahead and show the slide. Go ahead.

MR. SALMONA: Just the fact that what happened in '96, okay? This is '96 numbers, and this is a pharmaceutical gelatin in the U.S., of estimates. This is the pharmaceutical gelatin for soft capsule and hard capsule consumed in the U.S.

Should I take a microphone? Maybe.

CHAIRMAN BROWN: Microphone, please.

MR. SALMONA: Okay. So the global consumption is 9,700 tons for bovine gelatin and 3,700 tons for pigskin gelatin. If we focus on bovine gelatin, the local production which was used -- this doesn't mean this is as local capacity, but this is local production which was used in the U.S. in '96 is 2,000, the rest being imported, and 3,200 being imported from Europe as to lime bone, 1,000 tons to acid bond, and 1400 tons as to import hide gelatin, and the rest, 2,000 tons, being imported from other countries.

This shows the dependency of the American market on the importations. The situation, to be comprehensively honest, has been improved this year in terms of local production, because there has been some

capacity increase in the U.S. and, therefore, the number in '97 and '98 are likely to be a little bit less severe in terms of dependency versus importation. However, there is still a strong dependency.

CHAIRMAN BROWN: It puzzles me historically, since the U.S. has relative to Europe, so many cattle why this happened. I mean, we have more cattle probably than every -- than the entirety of Europe combined. Why are we dependent -- I mean, why was it -- Just out of curiosity, why was it that the gelatin manufacturing facilities were set up in Europe rather than this country?

MR. STRINGER: It's historic, and it probably has to do with collection procedures.

CHAIRMAN BROWN: It would sort of make sensible -- would be sensible to continue this change, I guess, wouldn't it? I mean, the source is here. We might as well manufacture it here.

MR. SCHRIEBER: I think I have to make one further remark to these numbers. A portion of this material, gelatin, coming from Europe into the United States is today already manufactured based on U.S. bones, because the gelatin industry has already started some years ago to import more and more degreased bones from the U.S. into Europe to

manufacture the gelatin in Europe, because there are the production capacities, and then to ship the gelatin back to the United States.

So we are taking basically every bone which is available commercially in the moment in the U.S. It's all used. To have more, again some more little tiny plants for degreasing might have to be erected somewhere in the U.S.

There might be still some quantities left which are not used today for gelatin manufacturing, but the other thing you have to keep in mind as well: You have a very big manufacture of photographic gelatin located here in the U.S., and this operation takes already 50 percent of the bones used here or manufactured here.

So a big portion is covered by photographic gelatin.

CHAIRMAN BROWN: Yes, but that's my point, manufactured here. It's a little like collecting coconuts in the Philippines and having the oil expressed in Switzerland.

DR. HUESTON: Can I ask -- I won't follow up the coconut one. So if I understand it correctly, the sourcing of the bones -- The slaughter plant, and then you go to the deboning facility, and at the

deboning facility the challenge is right now that all of the bones go into one bin. Right?

So the question is that, currently in the production capacity in Europe, there is not the facility for separating -- for physically separating the spines in one bin and the long bones in another bin. Is that what you're trying to describe to us?

MR. STRINGER: Well, additionally, the guidance specifies that it has to be removed directly after slaughter.

DR. HUESTON: Good. Well, let me get to that. So that if -- In other words, if the guidance said that it was removed at some point, then you could go to the breaker plants, and you could pick up long bones there without the spine being involved. Is that what you're saying? So it's only the fact of the hot carcass's immediate removal. That's the problem in the current guidance?

MR. STRINGER: That's not the only problem.

DR. HUESTON: That's a major problem?

MR. STRINGER: But that's a major problem. So relief from the directly after slaughter requirement would also --

DR. HUESTON: Would increase the

flexibility for sourcing the bones that are required to meet the guidance?

MR. STRINGER: That is correct.

DR. HUESTON: Is that what you're saying?

MR. STRINGER: Yes.

CHAIRMAN BROWN: Would anybody like to propose a motion to vote on? I'm a little puzzled as to what to propose. I sense that there could be a number of different proposals rather than simply say leave the question 1 and say yes and no.

Will, did you --

DR. HUESTON: Well, I was just looking. So it looks to me that one of the concerns here in this wording is that remove from the carcasses immediately after slaughter is one of the -- is causing part of the problem right now, as opposed to removed from the carcasses. I mean, that's a big part of the problem.

CHAIRMAN BROWN: Is the head of a carcass sawed off ordinarily? So someone in the slaughter house already has a saw, clearly.

DR. HUESTON: The difference is at slaughter, what they call breaker, where you're cutting the meat off the bone. I think that's the distinction.

CHAIRMAN BROWN: Well, that's a different matter. I'm just thinking -- Yes?

DR. HONSTEAD: The head is disarticulated with a knife. It's not sawed in this country.

CHAIRMAN BROWN: How do you get it off after that?

DR. HONSTEAD: Disarticulate the atlas from the base -- from the framena valley, framena and magnum.

CHAIRMAN BROWN: The knife does the rest of the work as well? I mean, you got to take the head away from the body.

DR. HONSTEAD: Then all you're left with is muscles and ligaments, and the hide has already been hided away. That all comes off. The hide has been removed. The hide is taken off the head, and then all you have is muscle and the atlantal axis joint, and that is undone with a knife. They're very, very quick and good at it.

CHAIRMAN BROWN: Okay. Was there some -- The reason I asked that question is, if there is already a kind of manually operated circular saw, I'm getting again at the possibility of just turning that saw around and going in two cuts down each side of the vertebral column to solve the removal of the vertebral

column.

DR. ROOS: But I don't think there's any problem in delaying the removal, if they're happy with that, Paul, and it sounds like --

CHAIRMAN BROWN: They're not happy. They're not going to be happy.

DR. ROOS: Well, they're not going to be happy, but it sounds like it's very difficult for them to do it, as they say, during the hot removal, and I think from a safety point of view, I don't see how we're compromising anything; because the dorsal root ganglia is tightly embedded in this spine, and waiting a day or two days or a week or at least a little bit shouldn't be a problem as long as the spinal canal is finally removed, the vertebra, and so it doesn't contaminate as a source material for gelatin.

CHAIRMAN BROWN: What was the reason that the FDA put the language in, to begin with? Does anyone recall why it was stipulated that this be done immediately after slaughter?

DR. ASHER: It was thought it would reduce opportunities for cross-contamination. If the final column is transected and left open with contaminating spinal cord for periods of time, it would present greater opportunities for the contaminating cord to

contaminate the rest of the carcass.

CHAIRMAN BROWN: Yes, but if the cuts were on both sides to get the column out, you wouldn't even -- the cord would be safely intoned.

DR. ASHER: That's correct.

CHAIRMAN BROWN: So I would agree that, if this -- We're talking about spines and spinal cords. We could change the language and say heads and vertebral columns and just, as you say, terminate the language after the word removed.

So if that seems like a plausible --

DR. HUESTON: Then I think we have the opportunity to wait, and I'm sure we are all very interested to see the results of the additional work that's been contracted for which the results will be presented ideally shortly after October of 1999.

DR. SCHONBERGER: Is there a way also to encourage them to use more of the raw material from BSE free places. They're saying that, if we say that they can't use material from BSE countries, that we create a big problem, but at the same time I would prefer that they not use material from the BSE countries as the starting material. Is there any way to encourage that direction without creating a major problem?

CHAIRMAN BROWN: Yes?

MR. STRINGER: We are striving to do that in every way possible. We're doing that, as you've heard, by the transportation of bovine bone starting materials from the U.S. to Europe and back.

I think the point that I'm making -- The only point that I'm making is that it's very tenuous. The supply chain is hanging on by a thread, and as the industry continues to grow or as interruptions to that supply chain occur, then we're left in a very difficult situation, but we're doing that to as great an extent as possible today.

DR. ASHER: I just want to make sure that folks not forget that, in addition to our previous concern about spinal columns, the new data from the MAFF which admittedly is limited now makes us concerned about bone marrow, and we would appreciate it if the committee would consider the issue of bone marrow as well.

DR. CHIU: I would like also to make a comment on behalf of the -- especially on behalf of CDER, Center for Drugs.

I think the committee should also evaluate whether the previous recommendation you have made, gelatins for pharmaceutical use, should come from BSE

countries. There is nothing to prevent you to revisit that decision.

CHAIRMAN BROWN: Well, perhaps we could have a restatement of the FDA recommendation at the moment. I have in front of me the slide that Dave prepared. At this time, with respect to gelatin, gelatin is permitted to be sourced from BSE+ or positive countries for oral and topical use with precautions. Is that correct?

Those are the precautions that are stated in our question. So the question is really restating the current FDA recommendation and asking if we still agree with it. Is that correct? Okay. Does everyone understand that?

The first question actually represents the current recommendation of the FDA, based in large measure on the recommendations of this committee several months ago. Right.

DR. ROOS: So we have this data regarding bone marrow that sounds, first, like they're tentative, but the other issue which maybe we addressed when we met before, but I don't remember quite so much, has to do with let's -- assuming that bone marrow is infected and during the preparation of gelatin, somehow I got the feeling that it gets washed

continuously for 40 days and degreased and so forth.

So I just would like perhaps some comment, if possible. I mean, what's the possibility that a little bone marrow is retained in this final processed product of gelatin? Should we be concerned about that? What's the feeling of the industry, assuming that bone marrow had infected material?

MR. SCHRIEBER: I just have to repeat what I have said before. Crushing the bones means changing the inside to become the outside. So this means, when you talk about long bones, the marrow is in the center of the long bones.

After the long bones are crushed, as well the bone marrow is sitting on the outside, and it will be washed away like the other CNS, what we have seen in our study. It will disappear from the surface of the bones, because we are still always talk about the surface contamination of the bones.

Everything which was mentioned which could be infective is surface contamination.

DR. ROOS: How much wash was there? What would be the dilution factor?

MR. SCHRIEBER: Until -- For example, I can only say this in the moment for our company. Until the gelatin goes to extraction, we have 28 times

change of solvent. Solvent is water, hot water, cold water, liming, acid, 28 times.

DR. ROOS: But let's say the volume of the bones to the solvent.

MR. SCHRIEBER: One to three about, one part bone and three parts water each time.

DR. ROOS: So it's like a one to six.

MR. SCHRIEBER: Yes, about 60 liters of water per one kilogram of bones.

CHAIRMAN BROWN: That's all included in your validation study, of course.

MR. SCHRIEBER: Yes.

CHAIRMAN BROWN: Yes. So all of these washes and the liming --

MR. SCHRIEBER: Yes. They were all there.

CHAIRMAN BROWN: -- and so forth knocks out about 2.8 logs of infectivity. Leon?

MR. SCHRIEBER: Oh, no. Excuse me. In the previous studies, what I explained before, at this time we only placed brain into the over-saturated lime solutions. There was no change of the lime, because then we would have washed away the brain. So in the previous studies, this was no change of water. This was just mouse brain placed in over-saturated lime or in this hydrochloric acid once, and sitting there for

the treatment period, no renewal of water or no renewal of lime in the old one.

The new one really runs the whole process, including all washing steps.

DR. OLANDER: You're washing study, the initial degreasing study -- you used three or four proteins to evaluate that as a proxy. Have you ever looked at the behavior, the comparative behavior, of these proteins to PrP-RES or scrapie PrP-SC, the stickiness, the aggregation ability within cancellous bone?

MR. SCHRIEBER: No. These marker proteins have nothing to do with infectivity. These are typical proteins which are part of the central nervous system.

DR. OLANDER: But then do they reflect the behavior of the PrP-RES?

MR. SCHRIEBER: I think this is unknown, because these are the only proteins which are really specific for CNS which we could use. So their behavior in relation to prions, nobody knows.

CHAIRMAN BROWN: Yes, that's right. It's a proxy. It may have nothing to do with it.

DR. OLANDER: My point.

CHAIRMAN BROWN: Or it may be a very

accurate reflection. It's just not known. Until you get an infectivity measurement, you won't know.

All right. So what we've got is raw material at the moment which, from BSE positive countries, might include raw material from BSE infected cow. Might.

As we speak, the material would include the vertebral column and bones, obviously. That's what's being rendered. Therefore, there's a possibility that there might be a very, very tiny amount of infectivity in the starting material.

We've also heard that in a model experiment which tries to reproduce an element or a stage or two in the whole process, that about close to 3 logs of infectivity is removed. We also know that there are other steps before and after which might have the potential -- have the potential and might truly again reduce infectivity further.

So we've got a little teeny possible bit of theoretical infectivity at the outset. We have a process which we know is reducing infectivity by at least 2.5 to 3 logs, assuming that the rigorous validation now in process in which real bones are going to be spiked, and a final product that is for use not as an injectable but as a topical applied

solution or as part of a pill or a capsule or oral.

That's the setting.

DR. SCHONBERGER: Did your 3 logs include the base step?

CHAIRMAN BROWN: Yes.

DR. SCHONBERGER: So there are some that only use the acid?

CHAIRMAN BROWN: Yes. We're not even going to talk about just acid right this minute. That might not be a bad thing to consider apart, but assuming we're talking now about the acid base full scale process, we should decide whether this language is appropriate or whether it should be strengthened or whether it should be relaxed.

DR. ROOS: One way to make this source material safer is to deal with a particular age cow, as I guess UK has done. One of our concerns, I guess, the last time -- and we hear it again this time -- is concern about jeopardizing the whole pharmaceutical industry and capsule production and so forth.

I just wondered what the impact would be if we had some age restriction as far as the slaughter of animals. In other words, perhaps -- I don't know whether the gelatin people could tell me as to how many animals are actually graded in 30 months of age

that get slaughtered and end up in gelatin production; and if we decided that we were only going to make gelatin from animals of BSE countries less than 30 months of age, whether in fact we could have a safer situation and also not jeopardize the industry.

CHAIRMAN BROWN: Linda?

DR. DETWILER: May I make a comment to that? Again, I don't know within Europe, but in the United States a 30-month period would be very difficult to do, because you usually have your younger than the breeding age, like your heifers and steers that go into your quality cuts, and then your older animals.

I don't know if that's a problem there, but I know here, and I don't know in Europe, that 30 months might be hard, because that's an in-between, and how do you know the bones from one versus another?

CHAIRMAN BROWN: Leon

MR. FAITEK: The people from the industry say that they generally can't use both acid and base processing at the same time. So the best that we could possibly hope for in the processing is 2.3 logs.

The other comment I wanted to --

CHAIRMAN BROWN: No. They said that a very small proportion of the total gelatin production

goes through only the acid process, that the overwhelming bulk of it goes through both the acid and base process.

DR. SCHONBERGER: That's my understanding.

MR. FAITEK: I'm corrected. The other thing is that we spent two pretty full days about a year ago going through all of this data, and we reached some decisions which I think were, to my way of thinking, more or less implemented by the FDA.

Now we're going through the same process again with essentially the same data, and if anything, I think the information that are provided by the gentleman from England, if anything, reaffirmed the decision that we made a year ago.

We're getting into a process of talking about public safety -- not talking about public safety. We're talking about what would be helpful to the industry, and I'm all for meat, but I think we're focusing away from what we're supposed to be focusing to. That is what's the safest thing to do?

CHAIRMAN BROWN: Well, the two pieces of new information that we did not have a year ago were a piece of pro information and a piece of con information. The con information is the fact that dorsal root ganglia have now been demonstrated beyond

any question to be infectious, and dorsal root ganglia are embedded in the vertebral column, and the vertebral column is included in the mix.

The good news is that the experiments, which were quite preliminary last year with respect to the amount of reduction of infectivity in the processing, are now much further along, and there's a fairly firm figure of about not quite a thousandfold reduction, about a seven hundredfold reduction in infectivity due to the acid based process.

These are two pieces of information we didn't have a year ago, and in large measure are responsible for our reconsidering the issue. As I say, unfortunately, one is -- I mean, they're opposing effects, but they are new, and I imagine we're asked to reconsider also because the industry came back to the FDA and said there are problems with it.

It is my personal view that we have no business considering those problems, as I've said time and time again. That's the FDA which is going to have to consider those problems. Our problems are to consider the scientific evidence and decide if there should be any change based on that.

DR. SCHONBERGER: Aren't we also getting some information from maybe Ray that the outbreak in

Europe is different now than it was a year ago in that we're seeing increases?

CHAIRMAN BROWN: Yes. Ray's slide was really very interesting. I hadn't realized myself that non-UK countries that have vastly fewer cases are, nevertheless, having increasing numbers of cases each year. So it's possible that there are quite a lot of incubating cases in other countries in Europe. So there's no way to know, but that was a very eye opening slide.

DR. SCHONBERGER: Yes. I mean, that--

CHAIRMAN BROWN: Which is one of the reasons, I'm sure, the USDA is now looking at Europe as a block.

DR. DETWILER: Paul, could we vote, maybe take a vote, just if we agree with our position from a year ago?

CHAIRMAN BROWN: Why don't we go back and vote on what Will suggested, which is just scratching "from carcasses immediately after slaughter." Is that reasonable? I mean, that has sort of been on the table for quite a little while now, and -- Yes?

DR. OLANDER: Just with respect to that, wouldn't it be reasonable to have the spinal cord right after slaughter out to prevent future

contamination as it moves through the processing stream?

CHAIRMAN BROWN: Well, the point is to get the spinal cord out, you have to either cut the carcass in half and lay the spinal cord open, which would be a worse situation with respect to cross-contamination, or make two cuts down, one on each side of the vertebral column.

DR. HUESTON: I believe they're already achieving it. In their presentation, they said they're already achieving it. So they have, in fact -- they're removing the cords immediately after slaughter. That's happening. So that's a given already. So the head is going. The skull and the brain are going, and the spinal cord is going.

The only difference would be that the vertebral body, the backbone, as it were, would leave later in the process at what's called the breaker plant rather than at the slaughter plant.

CHAIRMAN BROWN: Ray?

DR. SCHONBERGER: I was just wondering if, in order to get the concept that we would like to change the sourcing, which they apparently are trying to do themselves, to put in some encouragement and maybe even some time limit, like within the next two

years or something or a year and a half, that industry should go to non-BSE countries for their source material for gelatin that wills be used by Americans in these products.

CHAIRMAN BROWN: Yeah, well, the FDA when they look at the proceedings have what you just said in transcript. I think our vote should be on the question. We can express advice outside the question which, whether or not it's voted on, will be looked at and read and considered.

So I think the committee, obviously -- everybody in the room -- would love to see all of what we've been considering today from BSE-free countries. That's a given, and to the extent that that can be accomplished over the next near future, will be a plus; but I think we still have to vote on this question formally.

Can we do that now? I would ask the committee whether they want to vote on the first question with or without the last few words. That is to say, the stipulation that the spinal cords and spines be removed immediately after slaughter.

DR. SCHONBERGER: I think there was a consensus to remove it.

CHAIRMAN BROWN: Just to remove period.

DR. SCHONBERGER: Immediately after slaughter.

CHAIRMAN BROWN: Well, that's my question. Do you want to include that language or not include it?

DR. SCHONBERGER: Exclude.

CHAIRMAN BROWN: Exclude it? So the idea is that the sentence will end after the word carcasses, and the three last words will disappear from our voted question. All right? Everybody understand that? We're voting on the first question without the last three words.

The question is: Can healthy cattle from BSE countries -- da-da-da -- be considered a safe source of bones to produce gelatin intended for oral consumption by humans or for topical application to humans if the cattle are from BSE free herds and the heads, spines, and spinal cords are removed from carcasses?

Leon?

MR. FAITEK: Are you -- Is it your understanding in making this change that the spinal column is removed with two cuts?

CHAIRMAN BROWN: No, I'm not making that assumption.

MR. FAITEK: You're not making that assumption?

CHAIRMAN BROWN: No. I think it would be a good idea. Larry?

DR. SCHONBERGER Yes.

CHAIRMAN BROWN: Leon?

MR. FAITEK: No.

CHAIRMAN BROWN: Ray?

DR. ROOS: Yes.

CHAIRMAN BROWN: Bill?

DR. HUESTON: Yes.

CHAIRMAN BROWN: Linda?

DR. DETWILER: Yes.

CHAIRMAN BROWN: I vote yes. Don?

DR. BURKE: Yes.

CHAIRMAN BROWN: Barbara?

DR. HARRELL: No.

CHAIRMAN BROWN: Peter?

DR. LURIE: No.

CHAIRMAN BROWN: Doris?

DR. OLANDER: Yes.

CHAIRMAN BROWN: Beth?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: Tally is one, two, three, four, five, six, seven, eight to three.

Now I think you can take a minute or so and recommend any other refinement that you might want to do. We've already decided that it would be a good idea to try and go from BSE countries or BSE status unknown countries to BSE free countries. That's on the table and said.

Dr. Chiu wanted us to at least consider or discuss -- and I won't have this discussion very long -- about the possibility of bone marrow being infectious and whether or not that would influence us.

I think I could say as Chairman that we would like to once again see the topic of gelatin reviewed sometime within the next year when the bone marrow data will be more reliable and when the validation studies currently in progress or planned to start in a couple of months will be well along, and that will again be new information that may influence the recommendations of the committee.

So I would hope that the FDA would understand that our recommendations or our votes now are not to be considered written in stone and that, as new information comes up, we'll reconsider it. I know this is a longstanding policy of the FDA for all things.

DR. BURKE: If we do review the issue of

bone again, if it's at all possible to have data on the removal of marrow as has been documented for the removal of the nervous tissue, that would be encouraging to everybody.

CHAIRMAN BROWN: The second question is essentially the same question with respect to hides as a source of gelatin. Hides, as you know, is simply skin in animals as opposed to humans, and skin has never been a tissue from which any of the transmissible spongiform encephalopathy agents has successfully been detected, and it's been looked for.

It's been looked for in CJD. It's been looked for in BSE. I think it's probably been looked for in scrapie and has never turned up.

So skin as a starting point appears to be noninfectious, even in animals that are infected, and hides are also subject to processing which -- Does that include liming as well? I can't remember. The hides do. So it's also subject to a very effective decontaminating process, and if we need to discuss anything, we can. Otherwise, we can vote as quickly as possible.

DR. ROOS: It seems to me that there isn't any new data that immediately is different with respect to the hide issue since we voted on it last,

Paul, unless I'm mistaken.

CHAIRMAN BROWN: I think that's correct. So the question is: Can healthy cattle from BSE countries be considered a safe source of hides to produce gelatin for oral or topical use, if the cattle are from BSE free herds and contamination with CNS tissues and eyes is avoided?

Larry, your vote.

DR. SCHONBERGER: Yes.

CHAIRMAN BROWN: Leon?

MR. FAITEK: I abstain.

CHAIRMAN BROWN: Okay.

DR. ROOS: Yes.

DR. HUESTON: Yes.

DR. DETWILER: Yes.

CHAIRMAN BROWN: You're running ahead of me here. I vote yes. Don?

DR. BURKE: Yes.

CHAIRMAN BROWN: Pete? No, wait. Barbara?

DR. HARRELL: Yes.

CHAIRMAN BROWN: And Peter. Okay, now it's Peter's turn.

DR. LURIE: Yes.

CHAIRMAN BROWN: And Doris?

DR. OLANDER: Yes.

CHAIRMAN BROWN: And Beth?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: All right. That's ten to zero. So gelatin has now been disposed of, and we're actually absolutely on schedule. Does anyone want or does the FDA like us in five minutes or so to ask the same question we asked about derivatives of tallow with -- to now talk about glycerol? Okay. Glycerin/glycerol.

Okay. Do you want to do this before or after a break, committee? After? Okay, break time. We'll be back in 15 minutes.

(Whereupon, the foregoing matter went off the record at 3:32 p.m. and went back on the record at 3:49 p.m.)

CHAIRMAN BROWN: Committee members, the question of glycerin which we overlooked. Glycerin is neither tallow per se nor a derivative per se. It is an intermediate. It is a product that follows the saponification process.

Its substrate is tallow. It is a processed tallow, but it is not processed in the way that derivatives are processed. It is saponified, which means that it is exposed for a substantial

period of time to extraordinarily high concentrations of sodium hydroxide, minimum 12 normal, and you heard earlier today that, more often than not, it's a 50 percent solution.

We know that sodium hydroxide is one of the two or three chemicals which is most effective in reducing the infectivity of an aqueous solution of infected material. There follows a couple of distillation steps in which the material is subjected to high heat, but not under high pressure.

This is something that has never been validated, either in the laboratory or the field. That is, this kind of temperature applied to an aqueous solution at ambient pressure or even under vacuum, but it is more than likely that at 140-160 degrees Centigrade there would be again a substantial reduction in infectivity, although we can't put a number on it.

Then it undergoes a certain amount of purification to rid it of protein impurities.

As the FDA's position now stands, it is not allowed to be sourced from BSE countries, and our vote should, therefore, be, as it was for tallow and tallow derivatives, should it be allowed to be sourced from BSE countries.

You recall that for tallow proper the committee voted no, and for tallow derivatives the committed voted yes. Are there any questions at all before we take a vote on exactly the same question with respect to glycerin? David?

DR. TAYLOR: Just a comment, Paul, which might be a little helpful. You mentioned the process itself has never been validated. Just to let you know, I have some interim and incomplete data which I would not want to say was solid, but these relate to exposure of infectivity 2 molar hydroxide under conditions of microwave irradiation for, I think, about half a minute, and boiling for half a minute.

To date, the results are negative, but they are incomplete experiments.

CHAIRMAN BROWN: You say you've not detected any infectivity?

DR. TAYLOR: Yes. The animals are still -- Okay.

DR. OLANDER: How long are they on test?

DR. TAYLOR: Until something like 150 days beyond the normal maximum endpoint. I can't remember the precise model that we're talking about here.

CHAIRMAN BROWN: So again, preliminary, not absolutely a negative, but certainly you could

already say a reduction, certainly.

DR. TAYLOR: Yes.

CHAIRMAN BROWN: Which would be expected.

DR. TAYLOR: Yes.

CHAIRMAN BROWN: Yes, Leon?

MR. FAITEK: I know this is a toughie, but how much of a reduction in logs would you think it would take -- In your experiments where you reached the conclusion that there was no infectivity in a sample, what would you estimate the reduction in the infectious agent was at that point?

DR. TAYLOR: Depends on the model you are using, because the level of infectivity that achieved in the brain in different rodent models vary a bit, but we're talking about if you use the hamster model and you get no disease in the animals, you're usually talking about being able to say that you've lost something on the order of 7, 7 1/2 logs. With the mouse model it's right about 5, 5 to 6 logs.

CHAIRMAN BROWN: And that's correct. Sodium hydroxide has reduce infectivity by up to 5, 6, 7 logs exposed for one hour at one normal, and here we're talking 12 normal minimum, 50 percent which -- I don't know what normality that is, but it's enormous. Right?

MR. ROOS: So there are two parts to this. One has to do with the inactivation, which sounds pretty good, and the other has to do with purification; and that is a double distilling procedure, and my guess is that, from a chemical point of view, this stuff is extremely pure, and I don't know how pure. Maybe the chemists could tell us, but I guess 99.9 or something of this sort.

CHAIRMAN BROWN: Yes. What we've got is a tallow for which infectivity has never been demonstrated and two meat and bone meal, say, impurities at a fraction of a fraction of a percent with virtually no infectivity, and an enormous whack by the sodium hydroxide.

Did you want to add anything?

DR. WALKER: Yes. Just a couple of points. In terms of the caustic concentration, 12 moler --

DR. FREAS: Dr. Walker, could you identify yourself for the transcriber?

DR. WALKER: Yes. This is Dennis Walker with Proctor & Gamble.

In terms of the caustic concentration, the 12 moler caustic or 12 moler sodium hydroxide is roughly equivalent to 35 percent, and then, of course,

what is typical in the industry is 50 percent caustic, which could roughly equate to up around 17 moler.

In the FDA survey that we did of the 13 saponification manufacturers within the United States, 11 of the 13 used 50 percent caustic. There were two manufacturers that used 35 percent and 38 percent caustic, respectively, which, of course, would still meet the 12 moler part.

In terms of the purity of glycerin, glycerin is a very pure substance. As produced in terms of USP grade glycerin, typically it's 99.97 percent glycerol, with the remainder being water.

CHAIRMAN BROWN: All ready to vote? Larry?

DR. SCHONBERGER: I regard it as safe.

CHAIRMAN BROWN: Leon?

MR. FAITEK: What's yes and no on?

CHAIRMAN BROWN: Yes means it can be sourced from BSE countries with --

MR. FAITEK: Yes.

CHAIRMAN BROWN: Okay. Ray?

DR. ROOS: Yes.

CHAIRMAN BROWN: Bill?

DR. HUESTON: Yes.

CHAIRMAN BROWN: Linda, were you here for

that? We're talking about glycerin.

DR. DETWILER: Glycerin? Yes.

CHAIRMAN BROWN: Okay. I vote yes. Don?

DR. BURKE: Yes.

CHAIRMAN BROWN: Barbara? Not here? Okay. Peter?

DR. LURIE: Yes.

CHAIRMAN BROWN: Doris?

DR. OLANDER: Yes.

CHAIRMAN BROWN: And Beth?

DR. WILLIAMS: Yes.

CHAIRMAN BROWN: Consensus, ten to zero.

On to dura. Kiki, did you want to give us a charge or are we supposed to have an open public hearing first. I'm sorry.

In this segment, Bill, why don't you take the microphone?

DR. FREAS: For the last open public hearing, I have two responses that I received after the notice was posted in the Federal Register. Is Dr. Michael Joyce, President of the American Association of Tissue Banks here?

Dr. Joyce, you can either use that microphone or come up to the podium, whichever you would like.

MS. LOW: This is kind of -- Can you hear me? Can I --

CHAIRMAN BROWN: Can someone shorten that tube for Dr. Joyce? Thank you.

MS. LOW: Dr. Joyce was not able to make it, and I'm Jean Low, the Executive Director of the American Association of Tissue Banks.

The American Association of Tissue Banks was established in 1976 as a direct outgrowth of concerns among pioneers in tissue banking that allograft tissue be safe and effective.

This resulted in the development of the publication of standards for tissue banking that set rigorous performance requirements intended to prevent disease transmission and to ensure the optimum human performance of transplanted cells and tissues.

In succeeding years these standards have been revised to require ever more comprehensive screening protocols and the use of additional serologic tests licensed by FDA for screening for various markers of transmissible diseases.

The effectiveness of our methods of screening and testing is attested to by some noteworthy statistics. Over the past five years AATB accredited banks have distributed more than 2 million

allografts with no documented event of disease transmission from donor to recipient.

FDA and AATB have often cooperated in the presentation of workshops and symposia that address both scientific and regulatory events. We hope to continue this mutual support as more information is acquired about the pathogenesis of Creutzfeldt Jakob Disease.

Most of the recommendations put forth by the FDA TSE Advisory Committee and adopted by the agency are fully compatible with AATB standards on tissue banking and with the current procedures used in the recovery and processing of dura mater, and we readily agree with the FDA proposal to develop protocols controlling donor suitability and retrieval . However, there are two recommendations that pose serious impediments to maintaining the availability of dura mater for clinical application.

The first is the proposed requirement to test for presence of protease priori proteins using a test that's not standardized.

The second is the proposed requirement to archive a portion of the brain biopsy and retain a sample for 50 years. The technical liabilities of these two recommendations will be addressed in

submissions from Biodynamics International and the University of Miami tissue bank.

The Association simply wished to emphasize that these two requirements could so increase the difficulty and cost of supplying dura mater allografts that it would no longer be feasible to make these allografts available to transplant surgeons who use them for surgical repair in their patients.

We trust that FDA will assess the need to maintain the availability of dura mater for neurosurgeons and will consider whether protease resistant prion protein testing and archiving brain tissue for 50 years are so essential to patient safety that, if they are not performed, dura mater allografts should be eliminated.

The Association would stand ready to assist FDA in this needs assessment, if that would be a proper thing to do.

This assessment by FDA would be especially significant in light of the probability that thoroughly processed dura mater might be free of infectivity. Statistics suggesting that this might be true are rather compelling.

Worldwide, 63 of the 66 reported dura associated CJD cases have been attributed to dura

produced by a single non-U.S. firm. This firm did not screen donors for the presence of neurodegenerative diseases. However, it did allow pooling of tissue from a number of donors during processing, making cross-contamination possible, and finally, the company employed a disinfection procedure that was not known to be effective against the agent that causes CJD.

Dura mater produced in this country has never been shown to transmit CJD to a recipient of the allograft.

In summary, AATB welcomes every scientifically based approach to reducing any likelihood of reactogenic CJD transmitted by implementation of dura mater -- by implantation of dura mater allograft.

We believe that careful, thorough screening of prospective donors and the exclusion of those with any signs of neurodegenerative diseases, coupled with the use of rigorous disinfection of dura graft from acceptable donors and the prevention of the pooling of tissue from more than one donor will minimize any possibility of transmitting CJD.

Thank you.

CHAIRMAN BROWN: Thank you very much. The second presentation?

DR. FREAS: The second presentation is by Ms. Laurie Clarke from the law firm of Hogan and Hartson.

MS. CLARK: Gerry Oster could not be here today. So I am here for him. My name is Laurie Clarke, and I'm here as regulatory counsel to Biodynamics International, Incorporated, which processes Tutoplast dura mater.

I would like to read a summary prepared by Gerry Ann Oster, Biodynamics Director of Process Operations, in response to FDA's March 6, 1998, letter to the company concerning FDA's recommendations to incorporate additional donor suitability assessment, dura mater processing, and record keeping and tissue tracking steps into Biodynamics' procedures.

Biodynamics has created and maintained the highest standards possible to provide dura mater bioimplants worldwide, and has had no incidence of disease transmission in approximately 750,000 transplants.

Many of the elements recommended by the FDA and the TSE Advisory Committee are already basic tenets of the proprietary Tutoplast process and Biodynamics' quality standards.

Biodynamics has developed and implemented

recovery procedures which incorporate the American Association of Tissue Banks standards for determination of donor suitability and procurement techniques. Biodynamics' recovery manual states that dura mater should be recovered prior to removal of the brain biopsy sample.

Instructions state that caution should be used to avoid cross-contamination with all other tissue. Biodynamics prepares dura mater for transplant by using the proprietary Tutoplast process, which is described in the company's 510(k) notice for this FDA cleared product.

In brief, the dura mater is exposed to 1 normal sodium hydroxide for a minimum of one hour and then undergoes treatment with acetone. Thus, Biodynamics not only complies with the FDA's recommendation regarding dura mater processing, but also subjects the tissue to an additional viral inactivation process.

Biodynamics' procedures for recovery and processing are designed to minimize the risk of cross-contamination. Pooling of any and all tissue is strictly forbidden. Each tissue is processed separately. Disposal instruments are used when preparing the tissue for processing.

Each tissue is contained in a separate container labeled with a unique donor identification number, and gloves are changed continuously between the handling of each tissue.

Biodynamics maintains three sets of records in order to track the tissue from the donor to recipient. A master donor chart contains all records for donor. The process documents provide a detailed record accounting for each tissue during processing, and the shipping records indicate the distributor to which the tissue is shipped.

A tissue utilization record is provided with the allograft for completion by the surgeon following transplant. This document is filed by Biodynamics for future reference. All of the records can be cross-referenced to allow tracking of the dura mater from the donor to recipient and from the recipient to the donor.

In addition, Biodynamics has recently initiated new procedures for brain biopsy and will collect samples from no less than two sites from each potential dura mater donor, the frontal temporal cortex which the FDA recommended by sampled, and the posterior occipital lobe.

These samples will be of sufficient size

to perform histomorphological examination. Biodynamics has provided a copy of the standard operating procedure to FDA.

Brain biopsies will detect CJD after the onset of the clinical symptoms of this disease. Biodynamics supports the original recommendation of the TSE Advisory Committee to archive a representative sample of the processed dura mater.

Biodynamics has maintained an archive sample of every dura mater tissue the company has processed for transplant, and will continue to do so.

In the case of suspected transmission of CJD, Biodynamics would test the sample of the Tutoplast dura mater rather than the brain biopsy sample, because even if the brain biopsy sample shows evidence of CJD, the disease might be present in the Tutoplast dura mater due to Biodynamics' validated viral inactivation process, namely, the sodium hydroxide and acetone.

Moreover, Biodynamics has concerns and questions regarding the storage for brain biopsy sample at negative 70 degrees Celsius for 50 years.

Can a brain biopsy frozen at -70 degrees Celsius for 50 years be used for investigation of alleged CJD transmission? Will the tissue bank for

which the present brain biopsy will be stored be in existence 50 years?

What is the physical condition of the brain tissue frozen long term? Will thawing techniques allow the tissue to remain intact for examination?

Because of these questions, Biodynamics will retain a slide prepared for histomorphological exam of the brain biopsy with a pathological report as part of the master donor chart, but will not store brain biopsies.

Biodynamics also has investigated the availability of an appropriate PrP resistant testing methodology that may be used to screen potential donors of dura mater for CJD.

Currently FDA regulations require the donor specimens be tested using FDA licensed donor screening tests. Representatives of FDA have acknowledged that there currently are no FDA clear or approved test for diagnosing CJD.

The test methods available today are either investigational or for research use only. Thus, there currently is no PRP resistant test which has been validated for detection of CJD in human cadavers.

In addition, current research-only test detects CJD only when the clinical onset of the disease has manifested. For this reason, the use of the current tests, even if they could be validated, would not detect CJD earlier than next-of-kin interviews, medical history review, and/or histomorphological examination of brain tissue.

Therefore, Biodynamics believes that PRP resistant testing would be unnecessarily redundant of the other methods of proof in donor screening, and counterproductive due to the high likelihood of variable false positive test results.

Biodynamics does not intend to conduct PRP resistant testing at this time. The company will continue to monitor the development of specific tests for the detection of CJD at the earliest stage possible.

Biodynamics wants to emphasize its commitment to work with FDA to refine the company's processes and procedures when necessary, to ensure the continued safety and effectiveness of Tutoplast dura mater. Biodynamics' 25-year history of producing an estimated 750,000 allografts with no documented transmission of disease, including CJD, is evidence of the effectiveness of the Tutoplast process, as well as

the company's commitment to quality.

Thank you for the opportunity to address this committee.

CHAIRMAN BROWN: Thank you. Shall we vote? No. Kiki? Kiki Hellman is now going to bring us up to speed on FDA thinking.

DR. HELLMAN: Good afternoon. I am Dr. Kiki Hellman, Senior Scientist in the Office of Science and Technology in the Center for Devices and Radiological Health of Food and Drug Administration.

First of all, I would like to commend and thank the committee. This has been a very difficult two days dealing with different types of topics, and it has not been an easy one. I commend your endurance, and I thank you for deliberating on this issue.

This afternoon I'll present a brief background, current update, and proposed FDA course of action on the human dura mater issue, followed by the charge to the committee.

I would like to thank colleagues from the Center for Devices and Radiological Health, CDRH, and the Center for Biologic Evaluation and Research, CBER, who formed the working group on this issue, notably Doctors Jacobson, Albert, Whitten and Gaffe, and

Stephen Rhodes from CDRH, and Doctors Feigal, Asher, and Solomon and Jill Warner from CBER, and some of those folks are here this afternoon.

First of all, by way of background, because of reports of dura mater allograft related cases of CJD transmission in a limited number of recipients early in 1997 and the subsequent WHO recommended ban on the use of dura mater as an implant, together with Japan's Health and Welfare Ministry ban on dura mater use in brain surgery, the FDA TSE Advisory Committee was convened in October 6, 1997, to aid the FDA in its reevaluation of dura mater allograft and use relevant to the risk of CJD transmission; in other words, to assess the safety of using dura mater allograft for surgical use.

Since FDA had established safeguards and guidelines in 1990 to minimize the possibility of dura mater allograft related CJD transmission, and since there had been no confirmed cases of CJD transmission by dura mater in the U.S. since the guidelines were implemented, the FDA decided in March '97 not to restrict the distribution of dura mater cleared for U.S. markets and to consider any other appropriate action following the committee's deliberations and recommendations last October.

Next. At the October 1997 public meeting the TSE Advisory Committee considered (1) information presented about the risk of CJD disease transmission following surgical use of dura mater allograft; (2) the purported clinical benefits of dura mater allografts; and (3) the adequacy of alternative products in addressing its charge and to answer the questions posed by the FDA.

Next. After extensive discussion the TSE Advisory Committee recommended unanimously that neurosurgeons avoid the use of dura mater allografts whenever possible, but leave the final decision on the use of dura grafts to the discretion of the neurosurgeon, if the dura graft is processed following certain described safety measures.

Most of the safety measures that apply to dura grafts were already being implemented by the dura providers. At the October 6th meeting the Advisory Committee proposed additional safeguards intended to minimize the risk of CJD transmission through the use of this tissue.

They were: Histological examination of the brain of all donors of dura allografts; testing all donor brain tissue, dura donor brain tissue for PRP polymerase resistant protein, PrP-RES; archiving

a dura sample from each donor for reference and for further testing as needed; use of standards protocols for determining donor suitability and for harvesting dura; collecting the dura before brain biopsy; use of effective decontamination protocols; use of 1 normal sodium hydroxide for one hour should be a mandatory first step; preventing cross-contamination with other donors and other tissues from the same donor during processing and storage; developing methods for tracking dura from the donor to the recipient; and maintaining records for locating recipients.

After considering the TSE Advisory Committee recommendations and following extensive subsequent discussions among FDA staff from CDRH and CBER and between FDA staff and dura providers, FDA issued a letter to dura manufacturers recommending that additional donor suitability assessment, dura mater retrieval, dura mater processing, and record keeping steps be incorporated in standard operating procedures, and asking the manufacturers to respond describing how they planned to implement these recommendations.

With regard to donor suitability: (1) A sample of frontal temporal cortex of donor's brain obtained after -- should be obtained after dura mater

collection, 5-10 grams of tissue obtained for examination and testing, and the fixed stain tissue examined histologically by qualified neuropathologists for TSE changes;

(2) The brain tissue from each donor dura tested for PrP-RES;

(3) Acceptable donor dura must be negative for TSE histology and PrP-RES; and

(4) A portion of the donor brain biopsy should be archived to permit further testing to confirm potential dura related CJD transmission as new testing methods become available, the brain tissue stored at -70 degrees Centigrade for 50 years. The 50 years was arrived at after a discussion with Dr. Paul Brown and to be consistent with the current PHS draft PHS guidelines for xenotransplantation.

Finally, the provider distributor should be responsible for archiving the dura.

Dura mater retrieval: That industry and FDA accepted donor suitability and procurement protocols should be utilized when retrieving dura, and that FDA will work with tissue industry representatives to facilitate the development of protocols;

(6) Collect dura mater first before

obtaining the brain biopsy to minimize contamination.

Next. With regard to dura mater processing: Disinfect the dura by a method validated for effectiveness in minimizing the risk of CJD transmission, and for the ability to ensure clinically useful tissue based on data from an experimental animal model study. We recommended exposure to 1 normal sodium hydroxide for one hour, although an alternative processing method may also be used.

(8) No opportunity for cross-contamination of dura during harvesting and processing with other human or animal tissues should occur, and there should be no potential CJD contaminated -- no potential for CJD contamination of instruments during processing or storage.

Finally with regard to record keeping and tissue tracking, providers or distributors develop reliable method for tracking tissue from donor to recipient, and maintain appropriate records for locating each dura recipient in the future.

We received responses from the two manufacturers on March 31st, and you have just heard a summary from one of the manufacturers.

In the interest of time, the responses will not be presented point by point, although you've

heard some of them already. However, the concerns expressed by the manufacturers were taken into consideration by the FDA in proposing the following course of action:

Next. (1) Issue a revised letter to the manufacturers taking into consideration the manufacturers' concerns expressed in the responses to FDA and the comments offered by the TSE Advisory Committee at this meeting;

(2) Publish the revised letter in the Federal Register as general guidance, Level 1 -- that is, significant guidance -- to enable the opportunity for public comment.

Next, please. The following are FDA's considerations for a revised letter to the manufacturers, and they cover seven points as follows:

(1) The brain biopsy and histological examination: A full brain biopsy, including gross examination and, at a minimum, an adequate biopsy sample of frontotemporal cortex of donor's brain should be obtained after dura mater collection.

The histological examination, which is intended to identify evidence of TSE changes in the donor's brain, should be performed by a qualified neuropathologist.

(2) PrP-RES testing of brain tissue:

While reagents for PrP-RES testing are available from certain research laboratories, testing remains a research investigational use only tool.

There is no licensed or validated PrP-RES test for the screening of CJD in brain tissue. Nevertheless, a negative PrP-RES test is considered by experts in the field as significant in increasing the level of confidence that the brain and the dura are free of the CJD agent.

The FDA encourages the validation of PrP-RES testing as an aid in the determination that brain and dura tissues are not contaminated with the CJD agent. Manufacturers should continue to monitor scientific developments associated with the PrP-RES testing and should incorporate testing as a screening tool for dura mater donors when its usefulness for this intended use becomes apparent and the test itself becomes more readily available.

(3) What constitutes acceptable donor dura? Only dura mater procured from donors who have negative histories for TSE risk factors, have normal gross brain examination upon autopsy, and are negative for histological evidence of TSE changes should be considered suitable for transplantation. A negative PrP-RES test should be considered an additional

safeguard.

(4) Archiving of donor brain biopsy tissue: While archiving of donor brain biopsy tissue does not add necessarily to the safety assurance of the product immediately, collection of such tissue permits testing for TSE induced changes by new testing methods as they become available, and may later permit confirmation of potential transmission of CJD from a dura graft.

Providers of dura mater allografts should archive donor brain biopsy tissue at -70 degrees Centigrade for the shelf life of dura product. Further, the FDA suggests that a nationally supported archive for dura donor brain tissue be considered, since that would help to further the science of CJD transmission through dura mater grafts.

(5) Donor suitability and dura mater retrieval protocols: The FDA encourages dura mater providers and their professional organizations to reassess the appropriateness of existing donor suitability and dura retrieval protocols. Further, the FDA recommends that industry and government agencies reach consensus on appropriate industry standards and guidance in this area.

(6) Dura mater processing: The FDA

recognizes that sourcing considerations -- that is, donor suitability and dura retrieval, together with appropriate testing -- constitute the primary safety controls for dura allograft. However, additional processing safeguards, while maintaining the clinical utility of the product, may help minimize the potential infectivity of dura mater allografts.

The FDA recognizes that there is limited evidence that treating dura mater with sodium hydroxide will reduce CJD infectivity while preserving the tissue's clinical utility. In order to minimize even further the risk of CJD transmission, the FDA encourages the use of either a sodium hydroxide protocol or other procedure during dura mater processing that has been validated to reduce CJD infectivity.

Additionally, dura mater allografts must not be commingled at any step in the process procedure. Every effort should be made to eliminate even the theoretical possibility for commingling of donor dura grafts.

(7) Last, record keeping and tissue tracing: Each recipient of dura graft should be notified accordingly and a card containing all information on tissue sourcing, including the lot

number of the product, should be included in the recipient's hospital record.

Dura mater allograft providers are expected to maintain documentation of tissue distribution and identification of recipients. However, currently they are not expected to have the ability to track the recipient over time.

Manufacturers should continue to follow their standard operating procedures regarding donor suitability, processing, shipping and distribution, and tissue utilization record keeping that do not contradict the above recommendations.

Finally, our charge to the committee is to comment on the FDA proposed course of action concerning the safe sourcing, processing and use of dura mater allograft that is intended to provide additional safeguards for dura mater allograft while maintaining the clinical utility and availability of the product.

Thank you.

CHAIRMAN BROWN: Thank you, Kiki.

I thought the committee might enjoy a few sentences from the written responses of two or three organizations or people in the wake of our previous consultation. These are in the background materials,

but I'm not sure anybody has read them, and if they haven' t, 1'11 just select a couple.

From the University of Miami, a statement that consultations with a number of neuropathologists, Gambetti, Nelson, Rorke, parker, produced remarkably unanimous opinions concerning the value of histopathological examination of a large number of single samples of normal human brains in the hopes of detecting abnormalities.

The committee should read all this. It's pretty good stuff.

First of all, we ought to probably consider these proposals that Kiki showed slide by slide. I don't think most of them will pose a problem, but there's one problem, to begin with, and that is that either I and the committee did not communicate properly or the FDA didn't understand or deliberately made a slight change in what our intention was.

Our intention was never to use a 5 gram portion of frontotemporal cortex as the basis for neurohistopathological examination. Our intention was always to require a full neurohistopathological examination of every brain that was -- the brain of every patient from whom a dura mater was going to be

used.

That was misunderstood by practically everybody who responded. It was not just doing a neuropathology exam on that 5-10 gram sample. It was a full neurohistology autopsy examination.

DR. HELLMAN: Yes. We understand. When you do a full brain, you do a number of different samplings of the brain. That's right.

CHAIRMAN BROWN: Right. That should be specified in your letter, because even in the new proposals it's not clear that this involves a full neurohistopathological exam. You want to look at that language again.

DR. HELLMAN: All right. But then we had a teleconference with you in which we discussed the adequate sampling, and that's where the 5-10 gram came.

CHAIRMAN BROWN: Yes. The misunderstanding was that we were trying to make it as easy, so to speak, for the suppliers of dura as we could and still consistent with safety. That's where the 5-10 gram sample of frontotemporal cortex came in. That was for PrP testing.

In other words, instead of saying, okay, we're going to require 18 different locations for PrP

testing, we're going to make it just one, because this is where the PrP is most likely to be detected, if it's going to be detected; but the neurohistopathology, widespread and complete. Two different things.

DR. HELLMAN: All right. Well --

CHAIRMAN BROWN: That was misunderstood.

DR. HELLMAN: Okay. I understand, but then in this language the way it's stated here is we say an adequate biopsy sample of the frontotemporal cortex. You'd like that to be revised to indicate that there should be a full --

CHAIRMAN BROWN: That the neuropathology is full brain neuropathology, and the 5-10 frontal cortex sample is a kind of just special check for PrP. That's the misunderstanding.

Oh, good, you're still here.

DR. DETWILER: Can I ask a question, because there's a lot of things about the PrP RES testing, and I don't know about humans.

CHAIRMAN BROWN: Maybe we could -- Let's keep the questions for each of the points in turn. So for this first one, the language should state a full -- in my opinion. If anybody on the committee disagrees or has other comments, please pipe up, but

I would say a full brain autopsy including gross and histological examination, and put an adequate brain -- just leave that out. That doesn't belong here.

It should be a full brain autopsy, gross, and neuropathological examination, which should be conducted by a qualified neuropathologist, period. Nothing else belongs on that slide. Ray?

DR. ROOS: Yes. Just a comment, and that is one of the reasons that I think we were interested in this histopathological examination was -- had to do with issues regarding screening of the donors.

CHAIRMAN BROWN: Sure.

DR. ROOS: And questioning the donors, and how valid that was. I just want to repeat that, because I think that was really an impetus for us being concerned about this source material and the adequacy of any kind of history that we were going to end up with.

CHAIRMAN BROWN: Sure. What the respondees fail to recognize is that what we were doing was adding safeguards, not substituting safeguards. We weren't pretending that we knew that a neuropath examination on a clinically well patient would eliminate the possibility of CJD.

What we were doing was saying, yes, you've

got the history. Yes, you've got the clinical story. Now let's buttress that with additional safeguards, and none of them seemed to realize that. But one respondee stated -- can I say that without identifying the respondee, and just say -- because I mean, you're going to be basing your decisions on -- I mean, you've already based some of your decisions on the responses that you've gotten.

One objection -- can I sort of put it that way? One objection was that in some 17,000 autopsies a pathologist had never diagnosed CJD in a patient that was not diagnosed clinically, and this was felt to be a very strong argument for the fact that a neuropathology exam would be redundant.

My comment to that is that either in the area in which this neuropathologist practices, either CJD must come pre-packaged or something is going on, because everybody in the world who has had a lot to do with CJD has rarely but occasionally been surprised by making the diagnosis of CJD neuropathologically in a patient that had no clinical -- that clinically looked like something else.

So I don't buy that. I think that the neuropathology is not redundant at all, and that it should be included as you want it to be included; but

I think the first slide really does have to do with histological examination only, and so I would just, as I said before, indicate that a full brain autopsy, including gross and histological examination, should be performed by a competent neuropathologist, period.

Does anybody want to embellish that? I mean, that's a pretty clear statement of what we're requiring. Or does anybody think it's not necessary? I mean, we all did a few months ago.

Next slide. Linda?

DR. DETWILER: I just had questions, I guess, with animals. They question about PrP-RES testing in humans preclinical, but I wouldn't think that that would be practical for a study to -- right, preclinical, but in every animal species at least that I know of lab animals, that you can detect PrP-RES before you can detect histological changes.

That we know work for sheep, for sure. In cattle that were experimentally inoculated at Ames. Beth, is that the case, too, for deer and elk? Yeah. So I would think that the animals with all the models would show that it at least would be another safeguard.

My other --

CHAIRMAN BROWN: Does it relate to PrP?

DR. DETWILER: Yes, PrP. I mean, would you expect that would be the case with humans?

CHAIRMAN BROWN: I expect it might be, and I agree with you. You're not going to run around and take biopsies of 1,000 normal people to see if one is incubating CJD. It's just not done.

Experimentally, you're absolutely right. PrP can detect it at least often coincident with, if not before, neuropathology occurs, and neuropathology usually occurs halfway through the incubation period.

DR. DETWILER: Yes, and we -- in animals, it can be up to, you know, months and even years before.

My other question would be about -- that the test isn't commercially available. That -- Again, it's not in our realm as far as -- We have validated the test for animals, and we use it now as routine diagnosis for sheep with scrapie, but if the only demand is this kind of screening, would you ever have a validation or how would you go about it if it was so limited?

CHAIRMAN BROWN: Let me -- not rephrase it, but put a different orientation on it. Can the FDA invite a laboratory to be certified to test for PrP or do you depend on volunteers; because it's true.

I mean, if the FDA is not -- can't use this test as a requirement simply because they haven't got a certified test, how do we get a certified test?

There are plenty of labs who can do a good PrP test. How do we get one into the fold so that they can be certified, so that the test can be done?

DR. ASHER: It's not my specialty. I think all they would have to do is apply.

DR. ALPERT: I'm Susan Alpert. I direct the Office of Device Evaluation at CDRH.

The issue is that we don't regulate laboratories. We regulate the tests, and the issue for having a test that has been FDA cleared or approved is what we were focusing on.

We highly encourage, and that's what our language is intended to do, to encourage the development of validation of tests and the use of those tests, but the concern that's raised is whether or not tests offered in three or four laboratories where they have been in-house validated, in fact, give you the same information, and whether or not the test itself would be available as a marketed test.

So we are encouraging it. We are supporting it. We are recommending that the laboratories or that the provides of dura mater take

advantage of the information being developed, but we have, in fact, stopped short of requiring that a not approved or a test that has yet to be FDA approved be required by FDA. It's a bit --

CHAIRMAN BROWN: That's Catch-22. They don't have any motive for developing a test, because it's just going to cost them money. It's a bother.

DR. ALPERT: The issue -- Again, the issue for the FDA to stand and to be requiring a test that is not a validated or approved test is the cusp that we are --

CHAIRMAN BROWN: Well, that's the question. You need to get a test validated and approved.

DR. ALPERT: As was stated, they can -- A test can be brought in for clearance or approval, but until that time we have stopped short of requiring that these tests be used for this purpose. We are encouraging, but we're not requiring it. That's the issue.

I think that discussion about the quality of testing and an encouragement to develop testing is very important for us. I think the issue of the regulatory environment and what we can and can't do from a regulatory perspective is still under

discussion. But the approach we've taken here is not to require something that we have not approved.

CHAIRMAN BROWN: Yes. That is correct, and there's no motivation for anyone to approve it.

DR. ALPERT: The motivation is the one that, I think, we all agree is that it does add -- The motivation is the same -- I mean, I don't want to get into an argument or a discussion about why tests are developed.

The tests are developed because the scientific information is appropriate, important and useful. We are encouraging that this testing be done. There are -- We do develop orphan products. There are, in fact, benefits for orphan products. There is an opportunity.

This would, in fact, fit the qualification, I would believe, of an orphan type product, and there are mechanisms which can be used by the developers of tests to get those clearances and approvals, but our issue is to raise the concern and the question, and we can't force the laboratory to come to us. We can only offer the opportunity.

CHAIRMAN BROWN: Maybe one of the problems is that nobody realizes or few people realize that this test is a fully developed test. The responses

that you've been getting about this being a research and investigational test is just nonsense.

It's been used as a diagnostic test, published use as a diagnostic test, and to say that this is just not proven is just nonsense. So what -- and there are a half a dozen laboratories in this country that can do a valid test.

DR. ALPERT: We are -- Again, we're talking about two different issues. We are talking about what has been approved or cleared versus what a laboratory may have in-house validated. When we're talking about available approved or cleared test, we're talking about FDA approved or FDA cleared, legally licensed --

CHAIRMAN BROWN: How does the FDA approve it? How does the FDA --

DR. ALPERT: The laboratories bring their data to us, and we then evaluate whether or not --

CHAIRMAN BROWN: So it's voluntary.

DR. ALPERT: It's voluntary. The FDA does not have the authority to require a laboratory to develop a test and bring it in for approval. We're just not in that environment.

CHAIRMAN BROWN: Right. So just practically speaking, let us say a laboratory thought

that this might be a good profit making test, and they would say, okay, we will apply to the FDA to do this test so that the FDA can approve it. That's the way it will work. Is that right?

In other words, whether you approve this test will really depend on whether someone in a practical sense thinks they can make a profit on it.

DR. ALPERT: Let me raise two other issues. One is that, in order to provide any testing that is used as a clinical diagnosis, those tests have to also be overseen -- have to be performed in CLIA certified laboratories, which also looks at testing as it is used in clinical diagnosis.

Secondly, for tests to move in commerce prior to their FDA approval, they are not labeled for clinical use. They are not supposed to be used as the basis of diagnosis, and they move with the labels that we've just talked about, for research use only or for investigational use.

That's why the terminology has come up. It has to do with whether or not they are, in fact, FDA cleared or approved tests.

We also recognize that there are in-house home brew tests that are developed. Those are the ones that are overseen by the Clinical Laboratory

Improvement Act. They are in CLIA certified laboratories.

We don't -- We have not taken the position that it is appropriate for the FDA to be in looking at every single test that every laboratory develops, and home brew is, in fact, an appropriate way to develop and offer laboratory testing, but that's under CLIA.

To date, we are unaware of tests that are available that way. I think that's one of the reasons why we are putting this proposal out for comment, because these are very important issues that you're raising, and we would like to encourage laboratories to develop and have certified tests. Home brew is one way that they may offer an in-house test.

So it's not just FDA approval. There's also a CLIA certification process that can be used. We are unaware of any that have been made available in that way either.

CHAIRMAN BROWN: Well, thank you. If I thought that the test was really going to be useful in a highly significant number of patients, I'd push the argument further. I don't see much hope for this test for the next several years under these circumstances.

Leon?

MR. FAITEK: It seems to me that this

should fall under the CDC auspices, and I would think one way of doing that is issue an RFP, have a lab certified, and then let them go.

CHAIRMAN BROWN: I have no idea. It's a thought. Larry, what do you think about that?

DR. SCHONBERGER: That we should --

CHAIRMAN BROWN: Well, that a government agency ought to be certified as a tester instead of a private lab.

MR. FAITEK: They can contract it out.

DR. SCHONBERGER: I still think that the ultimate responsibility for licensing is FDA. CDC doesn't license these tests.

CHAIRMAN BROWN: The issue -- We weren't talking about licensing. You were just talking about a kind of brokering the development or the means by which this very good test could come to the attention of the FDA for what it is, a very good test.

MR. FAITEK: Once that's established, the agency or the contractor goes back to the FDA to get certified.

CHAIRMAN BROWN: Well -- Yes, Peter?

DR. LURIE: A question and, contingent upon its answer, a suggestion.

Are there any other areas, particularly in

the transplantation area, where FDA requires a non-FDA approved test? There aren't?

That being the case, I think, you know, Paul, what you're saying is right. I mean, it is a Catch-22 with regard to the market situation here, and I think that, if it's set up -- if the recommendation is set up in this, you know, "we suggest" kind of mode, it really provides someone who might otherwise come forward to the FDA to receive approval for the laboratory test with no guaranty of a market.

So it seems to me that, if instead we were -- this were written to say we'll require at the point that a laboratory test, you know, obtains approval, then it would create a real incentive.

Since there are, you know, any numbers of thousands of allografts a year, there's a guaranteed market of some size, and that at least would help somebody to come forward. Then we would be in better shape.

DR. ALPERT: One other approach that might be at least worth discussing, not so much here as in the proposal and out for comment by the industry, is that one other way of having tested validated is within a marketing application.

If one of the manufacturers were to come

to us, one of the providers of dura mater were to come to us with validated testing within their proprietary submission for what they use, that's another way that the test is used for the development of that product, but that's quite different than having it readily available for testing potential donors, if you will.

CHAIRMAN BROWN: Would it be permissible to use language such as Peter has suggested, which would say essentially what you're saying: We encourage the development and so forth of this test, and something to the effect of we'll require this as an additional criterion when such a test has been validated? I mean, would that be an appropriate way to deal with it?

DR. ALPERT: That was one of our intents, but I also think to keep on the table all of the other mechanisms by which test availability, whether it's within a proprietary submission or by service laboratory that has been otherwise certified by the government.

I think all of those are options for providing validated testing for PrP-RES, which is, after all, I think, the point of the recommendation.

CHAIRMAN BROWN: I'd leave out the research investigational phrase language, because it

really has been used as a diagnostic tool, FDA approved or not, and it's been a very effective tool.

It's up to you, but when I see research investigational, I know differently.

DR. HUESTON: Paul -- I mean, I take your point, but I'm not aware. Are there standardized protocol? I'm not aware that there are standardized protocol for PrP-RES that have been approved by any national or international organization.

CHAIRMAN BROWN: No, there's no approved protocol. Or actually, there may be, come to think of it. Herb Budka -- Herbert Budka in the Biomed II European-wide investigation of CJD has done work along these lines. Several different laboratories have been asked to test several different methods, and he's got results.

I don't know if they're published or not, but this is just to say that there is a study which is beginning and may already have been concluded to determine the best antibody, the best method, and/or the best antibodies, plural.

The other thing, I guess, that ought to be said is that immunostaining is not generally considered to be as sensitive as extraction of PrP and a Western Blot.

That was the reason for having a 5-10 gram sample, and that was based on the fact that, when we looked at 40-odd brains, including some brains from patients with fatal familial insomnia, we had a hell of a time detecting PrP, and we finally did when we used a large sample of brain from the frontotemporal cortex.

All of the cases that we had, which were clinical cases -- they weren't preclinical cases, but that was the reason for selecting frontotemporal, and that was the reason for selecting a fairly large amount, not for the histochemistry but for an extraction and Western Blot.

That would make somebody quite a lot of money, actually.

DR. SCHONBERGER: Does the sensitivity of the test, Paul, change very much by who is doing it? It's pretty consistent, isn't it? I mean, when you do it --

CHAIRMAN BROWN: I think it's getting quite consistent. There are still a half-dozen different modified protocols around and about, and different antibodies are in use, which is what Will was saying. There's no single test that everybody agrees is the gold standard, but there is a pretty

serious consensus that extraction by a method or another, followed by a Western Blot using an antibody that is as sensitive as 3F4 or using 3F4, is the best test.

DR. HUESTON: Let me take it another step. If I understand correctly -- and please correct me if I'm wrong -- If I understand correctly, the strong positives, most everyone agrees on, and the negatives most everyone agrees on. But there's this other group that accounts for -- I can't remember. It depends on the samples that you're looking at, but there's this other group of samples that come in there that they can't agree on whether they're positive or negative.

This goes back to some of the discussions we've had today about equivocal results. So that's part of the challenge. The whole framework of this discussion is here we have in the United States that we continue to allow the use of dura mater, which has been identified or recommended by the WHO to be withdrawn, and we are trying to -- We're trying to come up with some procedures to add some assurance that we're not getting infected dura mater.

CHAIRMAN BROWN: Well, I disagree. Maybe Bob wants to say something, too, about two of the three respondees and our most recent committee member

who is not here, Stanley Prusiner, saying that there was a problem with false positives.

I don't think there's a problem with false positives. There's a problem with false negatives. That's okay. A negative doesn't tell you you don't have the disease, but I've never found a positive in a patient or an animal that didn't have the disease. Have you, Bob? You haven't done many patients. I've done most of the patients. You've done a lot of animals.

DR. ROHWER: I've done very few human samples, but with the -- that big series you did on mice, for example, you do have to make an arbitrary decision as to what you're going to call a negative and positive.

It would be very nice to go back and look at all those things that are arbitrary and reinoculate them and say -- Unfortunately, we didn't collect the tissue in a way in which you could do that on that sample -- on that series -- but I do intend to do that in the future, because there is a point of arbitrariness in this assay, and it's exactly where you said it is, Bill.

DR. HUESTON: So the challenge you face is -- if I play devil's advocate -- Somebody is preparing

dura mater, takes it and three people test it, takes the one that the person that interprets it negatively calls it a negative or do they take the person that says, oh, gosh, I'm worried about equivocal.

DR. ROHWER: The other thing is there are -- I mean, they're all controllable, but the assay is also very sensitive to parameters like antibody concentration, the exact method you use for denaturation of the proteins, that type of thing.

So it can vary between laboratories. I think that's quite possible.

CHAIRMAN BROWN: Oh, absolutely. There's no question about that. We also looked, Will, at a series of 40 or 50 brains from patients who had been referred -- or that had been referred to our lab as possible CJD, which had histologically turned out not to be CJD, or -- Yes, that's correct. They were all negative. I mean clean negative.

DR. DETWILER: Can I -- As far as false positives, now we've done -- and we have scrapie endemically in the United States, and we recently did 500 samples from clinically normal mature sheep. See, I don't -- I'm agreeing with you, Paul, that I don't think there's going to be a problem with a high number, because even with a population that you have

an endemic disease, just screening those with -- in the Western Blot we use IHCN Western Blot -- it was just a handful that we had clear cuts.

You're right. We had some, you know, equivocal, but if I was getting a dura mater graft, would you want -- anybody here in this room want one of those? I mean, I wouldn't.

DR. HUESTON: But on the other hand, Linda, I agree with you wholeheartedly. The challenge is we all know there's differences in labs. So, you know, if you require this, the company sorts out, takes a lab that says, oh, reads everything negative. If you're in the business, you can always find labs with these investigational things that read everything negative.

CHAIRMAN BROWN: Well, let's - Can we -- Go ahead.

DR. ASHER: These are considerations with almost every --

CHAIRMAN BROWN: Sure. Of course.

DR. ASHER: So this is not really specific to PrP. Cut-off points, validation criteria for a satisfactory test, and criteria for accepting or rejecting a product are the stock in trade of people who work with these, and all these can easily be

overcome, as they have been -- and failure for labs to agree is common in many biological tests. It's not an insurmountable barrier at all.

CHAIRMAN BROWN: Well, let's -- Kiki, let's say that I think the committee is agreed that this is a potentially and probably really useful test, and just use any language you can for the strongest possible motivation to get the thing developed, standardized, approved, and used. Leave it up to you.

DR. BURKE: I'd like to ask what's done for corneal transplants now?

CHAIRMAN BROWN: I'm sorry?

DR. BURKE: What's done for corneal transplants?

CHAIRMAN BROWN: Nothing.

DR. BURKE: Would it also be appropriate?

CHAIRMAN BROWN: I once suggested that and got a lot of fan mail from the tissue banking people who deal with corneas. They have a better case, because they've put in a lot more corneas than the duras, and they've got a pretty good track record.

DR. BURKE: Well, if you're looking for a market, that was my question.

CHAIRMAN BROWN: Yes. Right.

DR. ROOS: I do think at some point it might be worthwhile for the committee to look into corneas, as well as other tissue transplants.

I wanted to comment that, in a way, this issue about positive/negative is perhaps the reason why we need good validation of this test in order to make certain that it's going to really do what we want.

DR. LURIE: Paul, I guess I have some ambiguity here. PrP-RES testing in the brain tissue - you're talking about Western Blot, because that's not clear.

CHAIRMAN BROWN: No, no. I would also encourage the language to suggest that PrP extraction with Western Blotting is what really ought to be developed, not immunostaining or not -- as a priority, Western Blotting, and at some point maybe they will develop an immunostain that's just as sensitive.

The thing is in that kind of flux, but at the moment Westerns are still the best.

DR. ASHER: We intentionally didn't specify what kind of test would be good to receive, because presumably ELISAs could be -- have been developed at least and could be satisfactory under some circumstances. Immunohistochemistry if --

CHAIRMAN BROWN: You might want to put a parenthesis then and sort of offer these choices.

DR. HELLMAN: That speaks to the point of what Dr. Alpert was trying to make. I mean, David is pointing out differences in sensitivity between the two types of approaches for detection of the antigen. So that's exactly what she was talking about.

So these types of things would all be laid out. We'd look at the data, and then we would be able to make a better assessment.

CHAIRMAN BROWN: I wasn't arguing about trying to get the best possible test by investigation and standardization. I was arguing about how it's going to get triggered.

Can we go on to the third.

DR. SCHONBERGER: Before you leave that one, this section did not mention the frontal temporal cortex, and you feel that's the --

CHAIRMAN BROWN: Number two?

DR. SCHONBERGER: In the 2, before we leave that. That's the section you feel is most likely to be positive.

CHAIRMAN BROWN: Unless you've got a test going, who cares? I mean, you don't even care about retaining tissue under these circumstances. If you're

not going to do the test, why retain the tissue?

DR. SCHONBERGER; No, I mean, if she's going to end up changing the wording on here that you want to bring to her attention, that --

CHAIRMAN BROWN: Yes. Should the test become available, at least one sample 5-10 grams from the frontotemporal cortex ought to be archived and frozen.

DR. SCHONBERGER: Right. That's what I wanted to clarify, that that go in there.

DR. HUESTON: Which tissue would be tested? This just says test tissue. We want to the frontotemporal to get in number two. That's the prime tissue for testing.

CHAIRMAN BROWN: In my opinion, yes.

DR. SCHONBERGER: That's what we were -- That's what I was addressing, and there is some data to suggest that that's the right section of the brain to look at for --

CHAIRMAN BROWN: If you're just going to say one, that's the one to say.

DR. SCHONBERGER: Right.

CHAIRMAN BROWN: I mean, you could require them to archive half the brain. Seriously, you would be better off. I mean, typically when we get a brain

that's interesting, we ask half to be fixed and half to be frozen, but that's a warehouse now.

The only thing here that I could think of, Kiki, was that there's no indication that among the negative -- among the TSE risk factors was a family history of neurological disease or that the patient themselves had neurological diseases.

Negative histories for TSE risk factors -- Maybe you could specify what they are. I mean dura mater, for example, is one.

DR. HELLMAN: Well, we can certainly do that, but I believe that the AATB and -- that certainly in those histories that would be covered.

CHAIRMAN BROWN: I'd like specifically to know that. Are donors for dura mater specified specifically not to have any neurological symptoms and to have negative family histories for neurological disease?

DR. HELLMAN: I believe that's the case, but perhaps Jean Low could speak to that.

CHAIRMAN BROWN: That's correct? Okay. As long as that's in there, that's good. I think that's all right as it stands.

DR. SCHONBERGER: But I think it should be in parenthesis and spelled out what the risk factors

are, because I think there will be confusion, just as in the other things, and it changes sometimes.

CHAIRMAN BROWN: Yes, sometimes it changes.

DR. SCHONBERGER: So it may well be worth in parenthesis --

CHAIRMAN BROWN: You know this already, but here they are again. Yes. Growth hormone receipt, dura mater receipt, negative -- or family history of -- That's another point. Is it family history of neurological disease or family history of CJD?

DR. SCHONBERGER: They've been asking about CJD, I believe, now.

CHAIRMAN BROWN: So blanket. Neurologic disease. Okay.

DR. SCHONBERGER: So any neurologic disease, even non-CJD, with the injection of the --

CHAIRMAN BROWN: Yeah, and that's -- But now that's --

DR. SCHONBERGER: That's okay.

CHAIRMAN BROWN: Yes, that's fine. That's your criterion. Is it also the criterion of the other company that produces -- Are they both here? That covers any --

DR. HELLMAN: AATB is the organization for the providers of dura.

CHAIRMAN BROWN: I see. Okay. So it's everybody. Okay.

DR. ROOS: I don't want to get too hung up on risk factors, but -- So that means that no relative in the family could have a stroke?

CHAIRMAN BROWN: Is that correct? Would you like to come --

DR. ROOS: Or have a post traumatic dementia or --

DR. HELLMAN: Excuse me. If you're interested in those types of questions, perhaps we could ask Jean to just specify what the criteria are. Come to the microphone.

MS. LOW: I don't have the standards with me, but it's neurological degenerative diseases, and that's the difference; and it is family members and so forth.

CHAIRMAN BROWN: So, okay. That's an important difference. Neurological degenerative diseases -- would that include, for example, multiple sclerosis?

MS. LOW: Yes.

CHAIRMAN BROWN: Okay. John?

DR. HONSTEAD: What about growth hormone treatments and other dura recipients?

MS. LOW: That's a specific exclusion now.

CHAIRMAN BROWN: Okay. Neurological degenerative disease. It would be interesting just for the record if -- Maybe you don't specify what they are, but I guess you do, since you mentioned that multiple sclerosis is included. Is it -- Have you got a list? I don't mean you, but I mean is there a list of neurological degenerative diseases?

MS. LOW: No. We have discussed a list, but we don't --

CHAIRMAN BROWN: So who do you depend then for on that -- for that diagnosis?

MS. LOW: The medical director has generally made those --

CHAIRMAN BROWN: Oh, whatever hospital the patient is in? In other words, you accept the diagnosis of the hospital in which the patient dies?

MS. LOW: Well, there's that, yes, but when the tissue bank -- medical director of the tissue bank releases that tissue, he or she has reviewed those hospital records, and if necessary, is consulting with the attending physician.

CHAIRMAN BROWN: Well, I think it's

possible for you to be fooled, but I think it would be very rare. I mean, you -- CJD --

DR. SCHONBERGER: Most of this is done, isn't it, by you actually interview the next of kin or is it from the hospital record or --

MS. LOW: No, it's mostly -- No, it's next of kin interviews, and actually most of this stems from HIV interviewing. That's where this close interviewing has really come from, but it's been -- This has had the optimum result of getting closer histories about CJD and other neurological diseases.

CHAIRMAN BROWN: That's a pretty good, pretty rigorous exclusion. I mean, you might have one in a million creeping through that didn't have the diagnosis of the degenerative disease that would turn out to have CJD, but it would be awfully rare.

What's the next slide? I have nothing to add to this. Does anyone else? Have a suggestion, Leon? This is the archiving question.

MR. FAITEK: No. This is the previous question. One of the handouts has a fairly comprehensive questionnaire that --

CHAIRMAN BROWN: All right. Okay. This is the archiving section. Right?

DR. ROOS: Yes. Maybe I'm mistaken, but

I think the advisory committee actually originally recommended archiving dura.

CHAIRMAN BROWN: That's misappropriated, too, I think.

DR. ROOS: Then that got changed by the FDA to archiving brain, which is where it stands now. I just wanted to open that up for discussion. It made sense to me from a safety point of view to take a piece of the tissue that gets implanted. In other words, I kind of like the idea that a little pieces of dura would be kept and stored and archived.

CHAIRMAN BROWN: Yes. I'm glad Ray brought that up, a good point. I don't see any reason why they shouldn't archive both, one for the possibility of reviewing it for diagnostic purposes, and the dura just in case anybody would like to try to transmit the disease. Yes, both brain and dura.

DR. HELLMAN: Yes. The reason this specifies the brain tissue is for the testing, as new tests become available, and many times you could pick it up in the brain and perhaps not in the dura.

CHAIRMAN BROWN: Oh, I think it's useful, and I think it's useful to archive both. I think the brain for testing possibly and the dura for transmission possibly. I think that would be the

ideal, and I don't think it would add to the volume of the archiving very much.

So is that agreeable, that we would recommend that both a small piece of that 5-10 gram piece of tissue from the frontotemporal cortex would be archived as well as a sample of dura, which I understand at least one of the companies is doing anyway. One company is archiving a piece of dura as a routine matter. Dave?

DR. ASHER: I just wanted to make a couple of comments, although this is not my primary center.

Although one always encourages the archiving of product, it's not clear if a recipient comes down with dura what can then be done short of doing animal transmission studies. I suppose an attempt can be made at PrP testing with the donor dura, whereas with brain it's clear what can be done with it to confirm the diagnosis in the donor.

It also should be made clear, the agency is well aware that the archiving is to serve to support the CDC look-back study. It would not improve the safety of the product. At least, it couldn't improve the safety of the product after the product shelf life was over. There would be nothing left to recall.

DR. SCHONBERGER: You know, at the last meeting I mentioned that we were investigating a case that is thought to be simply a chance association or coincidental association, but it possibly could be related. In that case, there is no dura or tissue available on the donor. That would have been very useful to have. But I'm wondering, if we had had that, if we tested it and it was negative, would you accept -- It's a business of proving the negative versus the positive.

If it was positive, I'm sure you would say, aha, that's the source, but if --

CHAIRMAN BROWN: It would just be another signpost in one direction or the other, but I mean, that's the way biology often works.

DR. SCHONBERGER: Right.

CHAIRMAN BROWN: I think that it's still valuable, and I think the dura should be saved. It's not just necessary for CJD. I mean, suppose there was a clostridium spore in there or something else.

When you're transplanting tissues and you have multiple pieces of tissue from a single sample, it's always a good idea to archive one. We wouldn't have been able to show, for example, that growth hormone was in fact responsible for the growth hormone

outbreak without growth hormone samples archived from every batch.

DR. HELLMAN: Exactly. I think we do agree with the principle of archiving, and that's why that second paragraph is there. Perhaps there should be some discussion between CDC and NIH for the wisdom of establishing a national archive for this purpose.

The other, thing which is a different point, is we do specify -70 degrees C for the shelf life of the dura product, and perhaps it would be helpful for the committee to confirm the fact that there is -- if infectivity is present in the original sample, that it would be present in a sample that's frozen at -70 degrees for a prolonged period of time.

To our knowledge, there is no study that has shown that specifically.

CHAIRMAN BROWN: Well, there's no study, but there's a lot of information.

DR. HELLMAN: Exactly. So if you could speak to that, that would be helpful.

CHAIRMAN BROWN: Sure. We've transmitted specimens that have been at -70 for close to 20 years. It's not something that you write a paper about, but that's a fact, and we're also talking about agents for which we earlier today have worried about surviving 12

normal sodium hydroxide and 300 degrees Centigrade.

So the idea that -- I mean, just intuitively, the idea that it would no longer exist after six or ten years at cold storage is just nonsense.

DR. HELLMAN: Well, the reason I wanted that to be made perfectly clear is because that has been brought into question, and I wanted it on the record by the committee.

CHAIRMAN BROWN: Right. Now it's on the record formally that at the NIH we have transmitted both CJD and scrapie that has been in cold storage for between ten and 15 years.

DR. SCHONBERGER: You know, I was just thinking of our case, Paul. We have a 50 year requirement. The case that we were just investigating, I guess, got operated on at age 68, I think, and 50 years would make him over 118 years old.

CHAIRMAN BROWN: I don't think we've got 50 years anymore, do we? It's just a shelf life of the graft. We're not going to require a 50 year archival storage.

DR. HELLMAN: Ideally, if one were to have a national archive, the samples should be archived for the lifetime of the recipient. It may or may not be

50 years.

CHAIRMAN BROWN: Ray?

DR. ROOS: With respect to storage, what do you think about the possibility of this being a -20 rather than a -70 storage?

CHAIRMAN BROWN: Don't know. I really don't. I imagine it's okay, but I just don't know. I don't think most -- I don't guess the tissue bank people have a problem with -70 as opposed to -20. Yes?

DR. TAYLOR: Just a quick comment, Paul. Like you, I think we have transmitted stuff that's been frozen for 20-odd years, but our standard is -30.

CHAIRMAN BROWN: -30?

DR. TAYLOR: Yes.

CHAIRMAN BROWN: Bob? You're going to have to alternate the microphone with somebody else than the lady in the back.

DR. ROHWER: I can say that we have -- We've titered stuff that's been stored for 15 years with no loss of titer at -- That's at -80. But my expectation is you could store the stuff under your bed.

CHAIRMAN BROWN: Yes, right.

DR. ROHWER: You wouldn't lose any titer

either.

CHAIRMAN BROWN: Exactly.

DR. ROHWER: I did want to make one point. We heard that there have been 750,000 of these grafts done. I don't know over what time period, but at 10 grams a graft or 10 grams a donor, that comes out to about eight tons of tissue. That's a lot of archiving at -80.

CHAIRMAN BROWN: If you held it for 50 years, yes. If you had a window, maybe --

DR. SCHONBERGER: Was that all dura mater grafts or was that --

CHAIRMAN BROWN: Dura mater -- The life of dura product is considered to be -- does anybody know shelf life of the dura? What's the shelf life of a dura product? No? So I mean, but that is what the FDA would like, the shelf life of the dura product, because it would allow recall of the rest of the product. Okay. Do you have any idea how --

DR. ASHER: -- because I tried to make clear that archiving permanently is to serve look-back studies the CDC attempts to clarify the whole situation. After the shelf life of the product is over, there's nothing for the manufacturer to do with the information that will improve the quality of the

product except change methods.

CHAIRMAN BROWN: Right. Does anybody have a ballpark idea of how long dura is kept on the shelf? It probably has a fairly rapid turnover. I mean, it doesn't have to, but my guess is it would.

DR. HELLMAN: I can't speak to that with any accuracy. So I would rather not say.

CHAIRMAN BROWN: Okay. The next slide.

DR. SCHONBERGER: For your information, by the way, Paul, the dura that was used in that 1985 case, I guess, was made in 1982. So it can be --

CHAIRMAN BROWN: At least a few years, right. Yes. Yes, and we know from Japan that one dura was certainly around for several years as well, because --

DR. SCHONBERGER: That's right, because it was '88 or something.

CHAIRMAN BROWN: Yes. Any comments on the fifth point here? I have nothing to say about it. Ray?

DR. ROOS: I think it would be nice if dura mater providers had some kind of -- You talk about consensus, but some kind of standardized written questionnaire that perhaps the corneal transplant individuals could use as well and, in fact, the whole

transplant community could consider.

I'm just bothered a little bit, and I think -- Maybe I'm wrong, but I think for the blood industry at present, there is something standardized and written as far as questions. Am I right? At least I think it would be good for the blood industry but also --

CHAIRMAN BROWN: The Red Cross, at least, yes.

DR. ROOS: Yes, some kind of consensus document that an advisory committee comes up with that people think is appropriate.

DR. HELLMAN: I think that your point is well taken. I think that efforts are already underway between the industry and the AATB to work on a standardized protocol. To the extent that that can be used for the transplantation of other tissues, perhaps that can be worked on.

CHAIRMAN BROWN: Next slide. I don't have anything to add on that either. I know that one of the responses to our recommendation for sodium hydroxide indicated that that was not always satisfactory and that it had acquired a certain stiffness that was undesirable. That was one response.

response.

We heard here that other people have felt that it was satisfactory, and we heard also that other neurosurgeons felt that synthetics were satisfactory. So there seems to be a whole spectrum of neurosurgical opinion about what constitutes a satisfactory graft material.

It seems to me the language takes that into account. All the FDA is doing is encouraging the use of a disinfectant protocol.

I will say that one respondee commented on tests using hydrogen peroxide and commented that it had been shown to reduce infectivity by 50 percent. That doesn't wash. That's not good enough. That's an arithmetic measure of a logarithmic function, and it has no use whatsoever. But you'll get additional information probably about that. I think that's not likely to be useful.

Does anybody have any comments or -- Yes, Larry?

DR. SCHONBERGER: Yes. Focus for a moment on the word commingled. We used that word to describe the dura situation, because they put the dural grafts all in the same container. So they were commingled.

In our investigation of this Florida -- in

Florida manufacturing procedures, and you go through it in detail, there is the possibility -- or there's some opportunity in some of the stages for fluid potentially that was in contact with one dura to possibly have contact with another dura.

I don't know if commingling catches that fluid through it or maybe we should change it to opportunity for cross-contamination of grafts.

CHAIRMAN BROWN: That's a good point. You might want to think, Kiki, about language that would say extreme caution ought to be exercised against the possibility of cross-contamination by any means, and that is quite right.

Fluids -- I mean, a container, for example, in which a graft had been stored is then emptied and not sterilized, and another graft is put in. The grafts aren't together, but there's every opportunity for cross-contamination. Yes, that's a good point, Larry.

DR. HELLMAN: That's good.

CHAIRMAN BROWN: Is that the last slide? Oh, dear. That looks all right to me, too. Very good.

I thank the committee immensely for their durability, and we -- Leon?

MR. FAITEK: There was one issue that came up. I don't know if the committee can address it. That's the prevention of importation of TSE agent for clinical -- for theoretical and research studies.

Is there anything that we can do to recommend that that be revoked or exempted or whatever?

DR. DETWILER: It's not -- That was not accurate. TSE agent can come in. It's under certain conditions. You apply for a permit through us.

MR. FAITEK: Okay.

DR. FREAS: Dr. Brown, members of the committee, invited guest speakers and guests, on behalf of FDA, I really would like to thank everybody for the long two days that they put in and all the preparation you had for this meeting. Thank you very much.

I would like to remind the committee members that we would appreciate if they would leave the confidential material on their desks, and I'll be around to collect it and shred it. Thank you very much.

(Whereupon, the foregoing matter went off the record at 5:23 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Transmissible Spongiform Encephalopathies Advisory Committee Meeting

Before: Food and Drug Administration/PHS/FDA

Date: April 16, 1998

Place: Bethesda, Maryland

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