Transcript of

Case: TSE Advisory Committee Meeting

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Neal R. Gross & Co., Inc.
1323 Rhode Island Ave., NW
Washington, DC 20005-3701

202.234.4433
fax 202.387.7330
info@nealrgross.com

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE (TSEAC)

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BETHESDA, MARYLAND

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WEDNESDAY
JULY 18, 2003

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

PRESENT:

SUZETTE A. PRIOLA, Ph.D., Chair

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

SIDNEY M. WOLFE, M.D., Member
CHARLES E. EDMISTON, JR., Ph.D., Temporary Voting Member
KENRAD E. NELSON, M.D., Temporary Voting Member
TERRY V. RICE, Temporary Voting Member
DAVID F. STRONCEK, M.D., Temporary Voting Member
SHIRLEY J. WALKER, Consumer Representative

STEPHEN R. PETTEWAY, JR., Ph.D., Non-Voting Industry Representative
SHEILA D. LANGFORD, Staff

ALSO PRESENT:

DR. ANDREW BAILEY, Plasma Protein Therapeutics Association (PPTA)
DR. STANLEY BROWN, CDRH
DR. PETER BURKE, AdvaMed
DR. CHARLES DURFOR, CDRH, FDA
LILLIAN GILL, CDRH, Senior Associate Director for Science

ELLEN HECK, UT Southwestern Medical Center
BENJAMIN HERBAGE, SYMATESE Biomateriaux
DR. CRISTOPH KEMPF, Plasma Protein Therapeutics Association (PPTA)
DR. RICHARD MARCHAND, University of Montreal, InoMed TS03
DR. GERALD McDONNELL, STERIS Corporation

CDR MARTHA O'LONE, Infection Control Devices Branch, CDRH
DR. ROBERT ROHWER, Director, Molecular Neurovirology Unit, VA Medical Center, Baltimore
DR. LARRY SCHONEBURG, CDC
DR. DOROTHY SCOTT, OBRR, CBER, FDA
DR. RUTH SOLOMON, DHT/OCTGT

DR. CHARLES WEISSMANN, MRC Prion Unit, Imperial College, London

I-N-D-E-X

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

(8:06 a.m.)

DR. FREAS: Good morning. I would like to welcome you back to this, our second day, of the Transmissible Spongiform Encephalopathies Advisory Committee meeting. I am Bill Freas, the Executive Secretary for this Committee.

I would like to go around and introduce again the members sitting at the table, and this will include the Temporary Voting Members who will be working with us today.

Starting on the righthand side of the room -- that's the audience's righthand side -- we have Dr. Pierluigi Gambetti, Professor and Director, Division of Neuropathology, Case Western Reserve University.

The next chair, which is empty right now but will soon be occupied by Dr. Richard Johnson, Professor of Neurology, Johns Hopkins University.

The next person present is Dr. Arthur Bracey, Associate Chief, Department of Pathology, St. Luke's Episcopal Hospital.

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

Next is Dr. Nick Hogan, Assistant Professor of Ophthalmology, University of Texas

Southwestern Medical School.

Next is Dr. Rima Khabbaz, Associate Director for Epidemiological Science, National Center for Infectious Diseases, Atlanta, Georgia.

Around the corner on the table is Dr. Charles Edmiston, Associate Professor of Surgery, Medical College of Wisconsin. He is also Chair of the Center for Devices General Hospital and Personal Use Device Panel.

The next seat is the Chair of this Committee, and that is Dr. Suzette Priola. She is an Investigator from the Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories, National Institutes of Health.

The next chair is our Consumer Representative, Ms. Shirley Walker. She is Vice President of Health & Human Services, Urban League of Greater Dallas and North Central Texas.

Next is Mr. Terry Rice, on the Board of Directors, Committee of Ten Thousand.

The next seat is Dr. Sidney Wolfe, Director, Public Citizen Health Research Group.

In the next seat is Dr. John Bailar, Professor Emeritus, University of Chicago.

Next is our Non-Voting Industry

Representative, Dr. Petteway, Director of Pathogen Safety Research, Bayer Corporation.

If you would at this time, double-check your cellphones to make sure they are either turned off or on the silent mode. We would appreciate it.

Also, yesterday we passed out over 200 survey questionnaires, and I really would like to encourage you, if you did get a questionnaire, if you would return it. The person with the questionnaires apparently has them locked in a safe overnight to make sure they are safe, and she will be here later on in the morning to give those who didn't get a survey questionnaire the opportunity to respond. So far we have gotten a total of approximately eight responses, and I really would like to get that in the double digits. So I would appreciate your cooperation.

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

CHAIRPERSON PRIOLA: Thank you, Bill. I think we will get started finishing up with the general introduction that we ended with yesterday on TSEs and decontamination. The first speaker is Dr. Charles Weissmann, who will describe his model for evaluating TSE decontamination of metal objects.

DR. WEISSMANN: Good morning. Thank you

for inviting me to present some of our results here. I will be talking of two results, the surface bound prion infectivity, which has a direct bearing on the processes for monitoring sterilization, and the second subject will be a new type of assay. Sensitive assay currently can be used for mouse prions and might be useful in this connection as well.

Next slide, please. So let me first talk about surface bound prion infectivity. This work was inspired by an incident in Zurich, where I was Professor for many years, where a 69-year-old woman was examined using an intracerebral electrode. I am sure many of you know this case.

The electrode, being a rather delicate instrument, was then very carefully sterilized or supposedly sterilized by washing it with benzene, 70 percent ethanol, and exposed to formaldehyde vapor for 48 hours. It was then used on a young female a few months later, and again washed in this fashion, and then used in a young male.

Twenty and, respectively 16 months later, these two individuals came down with CJD. As you know, very unusual at this young age. Meanwhile, it had been established that this first patient was suffering from CJD.

So it appeared that, despite this treatment, the electrode retains sufficient infectivity to pass the disease on in succession to two individuals. The tip of the electrode was then removed and sent to Gibbs in the United States who implanted it in the chimpanzee, and this chimpanzee then also came down with CJD.

This, as you see, was three years later. So the infectivity had been retained on that electrode for a long time.

This electrode was a rather complex instrument with wires and different materials on it, and some years later we decided to see whether one could reproduce this phenomenon in a mouse model. Next slide.

What we did here was to take a scrape-infected mouse two months before it would be coming down with the disease, and using a surgical steel wire to mimic an electrode, we then placed this wire for either five minutes, 30 minutes or 120 minutes into this infected brain. The wire was then washed with PBS exhaustively, and introduced into an indicator mouse permanently.

The same brain was then still homogenized, and a one percent sample was injected into the brain

of a mouse. These are special transgenic mice which have a shorter incubation time than normal mice, and the shortest incubation time one finds with this strain of mouse is around 65 days.

So this sample then caused the death of four out of four animals after 68 days. Astonishingly, this wire, even one which had been exposed for only five minutes, caused disease with the same incubation time, indicating that the dose -- the effective dose that was delivered by 30 microliters of one percent brain homogenate was similar to that delivered by a wire on which, as I will tell you later, we could not even detect protein.

Next slide. So five minutes exposure was sufficient to load this wire with a maximum amount of infectivity. The next question was how long does the recipient have to be exposed to such a wire in order for it to come down with disease.

So wires that had been exposed for five minutes in a brain were then left for only 30 minutes in the indicator or 120 minutes, and as you see again, all mice came down with the disease. Now you notice that the incubation time is longer than 65 days. So that reflects the shorter exposure time in this case.

The question then was: A wire which had

been infected by inserting it into a sick mouse, then used to infect another mouse for 30 or 120 minutes -- did that still retain infectivity the same way the electrodes did?

Next slide. This was indeed the case. A wire that had been inserted transiently and caused disease was then inserted permanently in a further indicator mouse, and you see that in both cases all mice again came down disease, and the wire was about as infectious as a wire which had just been dipped and not used to infect other mice.

So the amount of infectivity remained unchanged, despite the fact that this wire had been used to infect one set of mice. So again, like in the Zurich case, it would seem that there was no decrease in the infectivity of the wire after having been used to infect a mouse.

So -- next slide, please -- one can then use this system -- Well, you heard that yesterday evening. One can use this type of system to monitor sterilization procedures. This is just one experiment we carried out.

There is a group now at my institution, the Prion Unit, that is systematically exploring different treatments using this method. You see the

sodium hydroxide, one molar for one hour, was able to decontaminate the wire. Formaldehyde, ten percent for one hour, did not decontaminate at all. Guanidinium, thiocyanate, and autoclaving at 121 degrees was also effective; and a preparation of LpH, ten percent 90 minutes, was not effective.

I was then told by the STERIS people that this was a different formulation from what they have today. So maybe there will be some comments on that later.

Next slide, please. We then attempted to elute these wires with sodium hydroxide, just to see whether there is any protein that could be detected. We found no detectable amount. The limit of detection would have been 50 nanograms of protein per wire, and by the same technique, eluting with sodium hydroxide but then doing an immunoassay, we found less than 50 picograms of PrP per wire could be eluted.

So either the amount eluted is extremely small or else the infectious material is, more or less, irreversible bound to the surface.

Next slide. However, if you now take such a wire, expose it to a brain homogenate -- infected brain homogenate, wash it, and then detect -- look for PrP on the surface of the wire -- now this is just PrP, not specifically infectivity of PrP scrapie, but

just for the presence of PrP -- you can, in fact, detect the presence of PrP. But this experiment was not quantitative. It just tells you qualitatively that, despite the washing with PBS, exhaustive washing, you can still detect a layer of PrP -- whether it be PrPc or PrP scrapie, we cannot tell -- on the surface of this wire.

I might just add for the benefit of those who are not too familiar with this type of work that many surfaces, metal surfaces and other surfaces, bind proteins very avidly in a monomolecular layer. There is a lot of work which has been done on this subject, particularly in the milk industry where it is a major problem of proteins coating the insides of tanks and equipment.

So this is, in principle, a well known phenomenon that you can retain very stably a layer of protein.

Next slide. so this then raises the question which interested us very much. How does infection then proceed when you have a wire or metal surface that has been exposed to the infectious agent called prion.

So there are two possibilities. Either this infectious agent is bound tightly, but still

there is some release of free agent which can then proceed to infect the cells the usual way, whatever the way is -- that is also not really very well understood -- or is it so that the agent, while bound to the wire, can elicit infection?

I should perhaps add that it is believed that the infectious agent is a modified conformation of the protein PrP, and that at least part of the process underlying the formation of this infectious agent is a conformational change.

So the idea here would be that this conformationally modified PrP would induce conformational modification at the cell surface without having to leave the wire. So that if you then remove the wire, you essentially remove it as you put it in with the same number of infectious particles, but it is what we might call a hit and event. So it hits the cell. The cell becomes infected, but you can withdraw the wire without having lost any infectivity.

Now, clearly, this is a very difficult question to resolve, because whatever you do, you can always say you didn't look carefully enough for infectious agent that's been released. But we did do some experiments.

Next slide. The experiment is based on

using a N2a neuroblastoma cell line, which is more or less susceptible to infection by scrapie prions. From such populations, one can isolate highly susceptible cell lines, and I will come back to that.

Dr. Enari in our lab a couple of years ago isolated such susceptible cell lines and -- next slide -- he did then the following experiment. Oh, let me perhaps tell you how you can ascertain that a cell is infected by PrP scrapie.

We use a procedure which was developed by Bosque and Prusiner. So you grow a monolayer of N2a cells, susceptible N2a cells, expose them to prions, culture them 15 days with splitting, then plate them out on a cover slip and transfer the monolayer to a nitrocellulose membrane.

So when you pull this off, then the cell layer adheres to this membrane. You can dry it onto the membrane so that it is irreversibly bound. Then you treat it with Proteinase K. Now Proteinase K digests the normal form of PrP, but leaves behind the so called PrP scrapie. Whatever its functional role is, it is not important at this point, but it is a characteristic and reliably symptom of scrapie infection.

So after treating with proteinase to

remove the normal PrP, what you are left with is this abnormal conformer, and that can then be detected with an antibody and gives a stain on this filter.

Next slide. So what Dr. Enari did was to take a steel wire, expose it to infected brain homogenate, wash it, and then he placed this wire on a monolayer of susceptible cells. After a few days, one, two or three days, the wire was removed, placed in a separate petri dish, and the remaining monolayer remained in the original dish. This was then cultured for a further 15 days.

When the immuno-detection for PrP scrapie was performed, it turns out that only the cells which had adhered to this wire and multiplied during the course of these 15 days, showed PrP scrapie; whereas, even the neighboring cells did not.

So it certainly shows that intimate contact between wire and infected wire in the cells promotes infection, but this infection, obviously, does not at least spread very far from this wire. So our tentative conclusion is that intimate contact is required to elicit infection in the cells

Next slide. So here at the data. Let me just point out that these are the -- Here we have stained the cells. Now these are the samples where

there was a wire. You see that the cells have grown off the wire, and you see that it is only the cells that have grown off the wire that are positive; whereas, the monolayers which were left behind do not show evidence of infection.

Next slide. In a second type of experiment, Dr. Enari exposed metal disks to the infectious agent and then suspended the 1.5 millimeters over a N2a cell monolayer. In another parallel experiment, similar disks were covered with cells.

What was found then is that the cells, again, that had been in intimate contact with the metal surface showed evidence of infection; whereas, the monolayers underneath this metal did not, again suggesting that intimate contact between cells and metal surface is what promotes infection.

Next slide, please. We then explored this transfer of infectivity from surfaces to cells a little further. So again, the type of experiment is you expose this disk to brain homogenate, wash it, seed cells on top of it, and then transfer the colonies onto nitrocellulose, do this procedure, the PK digestion immuno-reaction, and see how many colonies, infected colonies, result.

Next slide. The first slide here shows you a comparison of using these cells on infected metal disks. Here are the number of cells which were then plated in order to determine the number of colonies.

So let us say, if you plate 5,000 cells that have been exposed to such a disk, you then find a number of infected colonies. Interestingly, a plastic disk made of a material called Thermanox seems to be more efficient in transferring infectivity to cells.

Next slide. We also looked at various types of plastic, polypropylene, polyethylene, Thermanox, polystyrene, and you see Thermanox was the most efficient. But this is an experiment which was only done once. So I wouldn't take the numbers too seriously except to recognize that plastics are at least as efficient in retaining infectivity and transferring to cells as metal is.

Okay, next slide. So in summary then, short exposure to scrapie infected brain renders these wires very infectious to mouse brain. One can use such infectious wires to monitor sterilization.

We were not able to detect any protein or PrP in eluates, but you can detect it on the surface.

The other important point is that both metal and plastic bound prions can infect subdural tissue culture cells.

Next slide. How much time do I have? Okay. I think this is quite interesting as a potential method for determining prion infectivity.

As you know -- next slide -- this has been discussed, I think, a number of times. Next slide. Infectivity is mostly determined by mouse or hamster bioassays, and there are in principle two approaches to that. You can inoculate a mouse with different dilutions of an unknown sample and determine the LD50 or you have also heard mentioned yesterday the incubation time assay.

There is a relationship between the concentration of prions and the incubation time. So this gives you sort of an absolute value, and the incubation time assay has to be correlated with this by the use of statins, but these assays are ones which are used for infectivity.

They take a long time to carry out. In the case of the hamster, the shortest time is 60 days but, of course, you heard yesterday that some hamsters come down even after 100 or 200 days. So you can't just stop the assay at 60 days. So, by and large, it

takes 100 or more days.

The same is true for the shortest mouse model, which takes about 60 days which is the minimum time at the highest dose.

Next slide. So we developed an assay which I won't -- I won't tell you how this all came about, but basically we call it the scrapie cell assay, and it is based on the finding that a single PrP scrapie-positive cell can be detected by ELISA, using a microscope, of course.

Next slide. The way we go about this is the following -- Of course, what is important is to isolate a very sensitive cell line. One of my collaborators, Dr. Peter Klohn, has now through several cycles of screening isolated very sensitive lines of N2a cells.

So what is done then, you make a tissue homogenate. You then make several dilutions, expose the cells to -- expose the sensitive cells to homogenate different dilutions, then wash it, expose it for three days to this solution -- two days would also be enough -- and then grow them and split them three times 1 to 10, for technical reasons which I won't go into now.

So after three 1 to 10 splits, the cells

are suspended, counted, and then one filters off either 100, 500 or up to 25,000 cells on a nitrocellulose filter in a 96-well plate. These are so called ELISPOT plates. So you filter off these suspensions, and the cells stick to the nitrocellulose. Then you treat them as before with proteinase K to destroy PrP, and then carry out an ELISA for resistant PrP -- remember, I told you that PrP scrapie is a very good diagnostic for infection in these cells -- and then you can count the number of spots.

Now, obviously, depending on the -- As I will show you, depending on the concentration of the homogenate and the number of cells you plate, you will, of course, get varying number of positive cells. As I will show you in a minute, we have to choose a situation where we have about 500 positive cells on a filter.

Now 500 positive cells -- they have to be counted, and that is, of course, extremely laborious. However, luckily, there is equipment which will do that.

Next slide. Let me first show you what such a 96-well membrane looks like when it has these positive cells on it. You see the positive cells.

You can see that it is quite laborious if you count that. We did that initially, but then we got this equipment, ELISPOT equipment -- next slide, please -- where you put the 96-well plate on the stage, and it automatically scans through these 96 wells, marks out all the positive cells, counts them, and the whole procedure just takes about a minute and a half.

Next slide. So here you see in a -- This is still a rather early experiment, not using our most sensitive cells, but you see that, for example, 10-4, 10-5, 10-6 dilution of the homogenate, and then plating 25,000 cells. So you can see -- readily see that, even at 10-6 dilution, you can still count a lot of points. The controls are virtually blank, not quite.

Next slide. So if you plot this, now you can plot the logarithm of the dilution against the logarithm of the spot number, and you get on this Log plot a linear relationship between about 10-7 to 10-5 dilution of RML brain.

The dotted line and the yellow line are two independent experiments carried out on different days, and it is really quite remarkable how well it agrees.

These plots here show so called resistant cells. So these are essentially the cells as you buy

them from ATCC, and you see that there is about two logs difference in the sensitivity. So now we are up to about 3 Logs with the newer clones.

Next slide. Now we can compare the sensitivity of the mouse assay with the tissue culture assay, and this is a mouse endpoint assay performed on the same homogenate as we prepared the scrapie cell assay. You see here the serial dilutions. You see that the LD50 is close to 10-7. You can calculate it to be 10-6.9, and at a 10-8 dilution with this number of mice you no longer detect infectivity.

You see in the scrapie cell assay, you still get a significant result at 10-7 and at 10-8, again you don't detect it. So by this criterion, the sensitivity is comparable. I must add that we are considerably better now with our newer cell lines than that, but here we are that 10-7 -- at a reasonable number of mice you have the same sensitivity.

Next slide. We then developed this scrapie cell assay to an endpoint format. As I will show you, this increases the sensitivity about tenfold.

Next slide. So this is based on the recognition that, if you infect a N2a cell and then culture it for 10 days, the infection spreads from

that cell to neighboring cells. So that you get an amplification effect.

So let us say you start out with one positive cell per 25,000, and then you culture these cells for 10 days or even 20 days. Then the proportion of positive cells increases very substantially, and this is shown here.

For example, in this experiment at 10-6 there was after 10 days culture time barely detectable infectivity. If you culture this for, let us say, 30 days, you already get 1500 cells rather than maybe 10 or 20 per 25,000. So the proportion of infected cells increases. You see that at 10-5 dilution also very clearly how the proportion of cells increases.

So we made use of that -- next slide -- to do an endpoint titration experiment. Let us assume that you have a suspension of infectious material, and you have, let us say, one prion per 100 microliters, and you dispense 100 microliters, let us say in this case, into eight wells of a 96-well plate.

So some wells will have one particle. Some will have two. Others will have none. Maybe one will have three. So this follows a so called pouisson distribution.

Now to detect one or two cells is

impossible, because the backgrounds are usually around 5 to 10 spots on such a filter. But if you now culture these for, let us say, two weeks, then this one per 25,000 cell will increase to 100 or 200 per 25,000.

So these wells then become strongly positive. But the ones which start out negative remain negative, and you can then use the pouisson equation. You just count out the number of negative wells and, using the pouisson equation, you can then calculate the average number of particles per 100 microliters dispensed, which in this example would have been .98.

Now when you carry that out in real life -- next slide -- you see here an experiment where we use a 10-7 dilution which, as I told you before, is an amount which can still be detected quite reliably in the ordinary scrapie cell assay.

Here we now use a 10-8 dilution, which we couldn't detect before with a statistically reliable way. You see in the case of the 10-7 dilution we use six wells, and the outcome was that one well out of six remained negative. All the others are statistically seen positive.

What you also see here are assays

performed after 12 days, 18 days, 27 days. So you see that, the longer you culture them, the more positive they get. But if they are negative, they just remain negative.

At the higher dilution, 10-8, we use 24 wells, and in this case 20 out of 24 were negative, or in other words, four of them were positive, and we now can calculate the average number of infectious particles per aliquot placed on these cells.

What we find here in the case of 10-7 dilution is 1.8, and at a 10 times higher dilution it is almost embarrassingly accurate at .18. So you can see that, while this is, of course, an accident that it's that exact, but anyway it demonstrates the principle that you can extend the sensitivity by carrying out the assay in this format. It takes longer, and you have to use more wells per sample.

You could also extend the sensitivity of the mouse endpoint assay by using more mice, but no one is going to use 50 mice per point -- per experimental point, and it's easy to do on cells because the assay, as I have told you now, can be automated almost completely, because all those steps are carried out in 96 well plates.

Next slide. So in summary then, an N2a

subclone DAT-8 is highly susceptible to mouse prions, and the scrapie cell assay is based on the detection of single scrapie infected cells using ELISPOT technology.

This assay is at least as sensitive as a mouse by assay, but ten times faster and two orders of magnitude cheaper and, as I mentioned, it can be automated.

Finally -- next slide -- I would like to introduce my collaborators. Eva Zobeley at the University of Zurich started the wire experiments. They were continued by Eckard Flechsig in London, and my colleagues Peter Klohn, Lars Stolze, Sukhi Mahal, and Therese Solstad, contributed to the work on the scrapie cell assay. My host in London is John Collinge who has been extremely helpful and kind in supporting our work, and Adriano Aguzzi at the University of Zurich has been very helpful with ideas and material. Thank you.

CHAIRPERSON PRIOLA: Well, thank you very much, Dr. Weissmann. Questions from the Committee?

DR. EDMISTON: I have a question. That was an excellent presentation, and I think it really dovetails very nicely with the presentations we had yesterday afternoon.

There are two points that come to mind when I listen to your presentation. First of all, from an endpoint threshold perspective, your studies would suggest that it would be very difficult to ascertain endpoint threshold, especially in the case of those wire studies, in that if a true threshold is something that we are gearing for, you would be talking about zero; because talking about a zero threshold in light of what your studies have shown in stainless steel.

Extending that to other metals or other finished products, have you been looking at that in terms of gold, titanium, and other types of --

DR. WEISSMANN: We looked at gold, and gold is as efficient as steel. But we haven't extended it yet to other metal surfaces.

DR. EDMISTON: The second point I want to make -- again, this is something we all need to be thinking about for the rest of the day -- is the issue of validation studies concerning either in vivo or in vitro assays.

I think that is an extremely important point here in terms of being able to validate whatever sterilization, disinfection protocol we wish to endorse ultimately out of all this.

Now let me ask you this question. Let me ask you a personal question.

DR. WEISSMANN: Sorry?

DR. EDMISTON: Let me ask you a personal question.

DR. WEISSMANN: Yes.

DR. EDMISTON: This is not a scientific question. This is a personal question.

How comfortable are you with the World Health Organization guidelines as they stand from the practical perspective of laboratory and patient and health professional safety?

DR. WEISSMANN: Fairly comfortable, fairly comfortable. I think it's extremely difficult to assess what the -- For example, in Great Britain where there is fear that there may be variant-CJD cases which have not been diagnosticized and which might be the source of infectivity if surgical instruments are used. I think that the procedures which have been recommended are probably -- If you consider the theoretical risk and the efficiency of the methods, I would say that I feel fairly comfortable.

Now it's impossible to say I feel totally comfortable, because, as you point out yourself, there is no real endpoint. You know, one can see that in

mouse experiments and also in tissue culture experiments. Usually, infected mice come down at a certain time point. Let us say the CD1 come down at 150, but if you wait long enough an occasional mouse will come down after 200 or 300 days, and this a stochastic effect.

So if you want to be completely safe, you would have to keep these mice until they die, and even that is not enough, because we know that some mice can carry a substantial load of infectivity, and yet remain clinically healthy.

So in the sense of -- In that sense, it's very hard to say that something is totally efficient.

DR. EDMISTON: So I think, for the purpose of the Committee and the people in the audiences, we are always going to have an issue of acceptable risk, aren't we?

DR. WEISSMANN: Well, that's life, isn't it?

DR. EDMISTON: Right. But I think that is important to point out, because we are dealing with an entity that is going to be virtually impossible to eliminate with any high degree of certainty.

DR. WEISSMANN: Absolutely. I was just thinking, you know, that the question of blood supply

-- You may get to a point where you are so stringent with the regulations of what to accept that in the end you lose more patients because the blood supply is insufficient, as you might preserve from eliminating a one case in 10 million or preventing one case in 10 or 50 million.

So it's a trade-off, and one has to bear that in mind.

DR. EDMISTON: Thank you very much.

CHAIRPERSON PRIOLA: Dr. Wolfe.

DR. WOLFE: An excellent presentation. It reminds me of the excitement of being at NIH to see some of these experiments again. Two questions.

One: Was there ever any attempt in whatever way possible to go back to those unfortunate human experiments with the EG electrode and get some rough order of magnitude calculation as to how many cells might have been or how much -- You said the limited detection was less than 50 picograms eventually. But how much would that translate into in terms of human tissue? That's the first question.

The second is: If you were running a hospital, knowing what you know from your experiments and knowing what at least most hospitals, let's say, in the United States where at least thus far we

haven't had any cases of variant-CJD -- But if you were running a hospital, what way would you alter the procedures in a typical hospital based on what you have learned in your experiments?

DR. WEISSMANN: Well, as I do not know what the routine is in hospitals in the United States, I can't really answer the question.

DR. WOLFE: What would you do anywhere, knowing what you know?

DR. WEISSMANN: I would use a sterilization procedure, let's say, at 135 degrees, 20 minutes. But I would also -- and this is something my unit, the unit I work in, is working on. I would use a two-step procedure. I'm sure a lot of people are doing that or contemplating doing that, a first one being a detergent enzyme treatment to remove the bulk protein which is bound to these instruments.

There are ways of doing it which, I think, are quite compatible with hospital routines, which would mean soaking the instruments before they have had a chance to dry down the blood and tissue, immediately place them in these solutions which are quite innocuous, so they can be kept in an operating room, and soak them in there and heat them -- take them out, heat them for an hour at a specified

temperature, then rinse them, and then go through the autoclaving procedure.

This type of procedure is what I would recommend.

DR. WOLFE: Is this being done in the U.K. or is this --

DR. WEISSMANN: No, this -- Well, again, you know, I don't know what all individual hospitals do, but this is what our unit is aiming at.

CHAIRPERSON PRIOLA: Dr. Gambetti?

DR. WOLFE: And the first question, just any estimate on what was on those wires?

DR. WEISSMANN: No, but you touch, of course, on a very interesting question, which is why are virtually undetectable amounts of material as infectious as injecting a suspension?

Now sometimes I am asked, is it possible that the wires have a preferential affinity for infectivity, so they sort of concentrate infectivity. I don't think that this is the important feature.

Experiments tell us that, if you inject brain homogenate, infected brain homogenate, into a mouse brain, then most of the infectivity disappears within three days. It's virtually undetectable. So there are mechanisms in the brain which somehow manage

to degrade this injected material. So the infectivity actually drops.

Now if it is absorbed to the surface of a wire, it is probably protected against, let us say, phagocytosis by microglia or maybe even by tissue enzymes. So what I believe is that, when the infectivity is on a wire, it is stable on it for maybe days, weeks or even months. These wires were implanted for the lifetime of the mouse.

So if you talk in pharmacological terms, the area under the curve is very large, even if the dose is not very large. Whereas, if you inject the homogenate, you get a high spike, and then it disappears very quickly.

So that is why I think that these wires are so particularly infectious.

DR. GAMBETTI: It is always of great interest to hear this work for me. So I compliment again for this excellent work.

Echoing a previous question, one listening and looking at your data gets the impression that there is kind of a fatal attraction between the wire that you use and the prion, infectious prion protein. It looks like really there is a tendency for either the infected cells or the prion itself to stick to

that wire and stay there indefinitely.

So the question is -- and it was, I guess, asked before -- whether you think there is a way to eliminate this affinity without, of course, using the -- without losing the use of whatever instrument could be available with that particular stainless steel. I understand the whys of stainless steel. Could, in other words, one eliminate this affinity without losing the use of an instrument made of that? That is one.

The second is: Did you try to investigate by, for example, metal electron microscopy, how is really the arrangement of the epitope that you demonstrated on the wire at the structural level, and whether this would change with changing the material by which the wire is made?

DR. WEISSMANN: Well, let me start by saying we have not investigated the surface of the wire by electromicroscopy. Just ordinary electromicroscopy would probably not yield much information, because we are using crude brain homogenates, and there's a lot of proteins stick, you know. So you would see a lot of things which have nothing to do with infectivity. So we haven't done that. We haven't done this experiment.

The first part of your question, whether one -- What I understand you are asking is, is it possible to treat the metal surface in such a way that it no longer binds infectivity?

We have not yet started these experiments, but I believe this is a very -- would be a very attractive possibility to coat the metal surface in such a way that it loses the affinity for the proteins.

There is a project which has been formulated and which will be carried out, but it hasn't even started yet.

CHAIRPERSON PRIOLA: Dr. Bailar.

DR. BAILAR: I can imagine an experiment in which you determine a method that results in a very low infectivity of the needles -- maybe half the needles are infectious, and half of them aren't -- and that those are then implanted serially in mice to see whether the infectivity diminishes with successive implantations. Has anyone done that?

DR. WEISSMANN: No. I think it's a very good idea, but it hasn't been done.

May I just make a comment? I think all these assays provide us with guidelines how to go about sterilizing. It is my opinion that, before one

really recommends a procedure as being valid, it has to be executed using BSE agent or variant-CJD agent, and it is my opinion that it has to be done in a primate experiment.

CHAIRPERSON PRIOLA: If I can ask one question along those lines. What do you think is the potential for your assay to be adapted as an in vitro assay for detection of human CJD, variant-CJD, BSE? It's a very difficult prospect, I know, in tissue culture.

DR. WEISSMANN: Yes, we have people who have spent considerable time already looking for cell lines which are susceptible to human prions or bovine prions, so far without any success. I mean, you certainly are aware of the fact that these cell lines have this peculiarity, that they don't even respond to all strains of mouse prions. I mean, this in itself is enormously interesting, but not very helpful.

CHAIRPERSON PRIOLA: Okay, thank you very, very much, Dr. Weissmann. That was excellent.

Our next speaker will be Dr. Cristoph Kempf, who will discuss again some TSE decontamination and validation studies.

DR. KEMPF: Good morning, ladies and gentlemen. Thank you very much for the introduction.

We have heard yesterday and already this morning that some agents like sodium hydroxide or hypochlorite can be efficient in eliminating prions. However, we also have learned that, for example, drying is not good for sterilization or decontamination of equipment.

I think one of the main points I heard yesterday was from Bob Rohwer, and may I have the first slide, please. You have already seen this summary. In many cases, sodium hydroxide is very efficient. However, there are single point measurements or other measurements that showed us residual infectivity.

Bob Rohwer mentioned that it is mainly the first phase which tells us anything about the PrP, or the prime protein, which is thought to be the infectious agents, and the residual infectivity, the second phase, that in activation kinetics is foreign, is more due to environmental conditions or experimental conditions.

So we addressed, since we are dealing in the industry with large equipment, the effect of sodium hydroxide and hypochlorite, and I will show you several experiments that were performed.

One of the questions we asked: Do we

really need these high concentrations, because that is not exactly what you like in a facility due to occupational health, dealing with 0.1 normal sodium hydroxide for the work. It's not the best to do.

Next slide, please. So one of the first experiments that was performed was to look at PrP resistance to proteinase K. What was done in this experiment, hamster brain homogenate at the final concentration of one percent was incubated for various times at different temperatures and at different sodium hydroxide concentrations.

After given times, it was tested for PrP resistance or proteinase K resistance. As you can see, no cases where the tests were done, there was no signal detectable, and here the gray part like 0.1 normal sodium hydroxide, at 50 minutes you couldn't find any Western blot signals. Shorter times were not tested.

In the next slide, we have a similar experiment, again with 0.1 normal sodium hydroxide incubated for 50 minutes, 60 minutes, this time with liposomes purified from scrapie infected hamster brain at room temperatures. You can see, after 60 minutes, no symptom was detectable. Debatable if this is still the same or if it's carryover. Whereas, an incubation

in PBS, phosphate buffered saline, showed a nice dilution.

The next slide, we investigated the kinetics with different and even lower sodium hydroxide concentrations. To our surprise, at extremely short times, like 10 seconds, you saw a clear decrease of the Western blot signal PrPres. where the proteinase K sensitivity is not anymore here, and after 15 seconds we detect only two legs, and after half a minute at 0.1 normal of sodium hydroxide we lost all the PrP signal.

The next slide summarizes these experiments. Each curve represents triplicate values, and you see the inactivation kinetics. At 10 millimole there is little inactivation of the PrP res. or destruction of the PrPres. Whereas, at 0.1 normal rapid destruction of PrPres was observed.

The next slide shows similar experiments performed with sodium hypochlorite. The preliminary results are shown here. You can see that also was very low compared to the active chloride, 100 ppm. PrPres -- Sorry, the PrPres starts to disappear after half a minute, one minute, five minutes, 15 minutes. We were unable to detect any residual PrPres expressing these kinetics.

Now with this experiment we have to be very careful, because in control also PrPc could not be detected. So it could be that we just mask the epitopes that are used in the Western blot for the detection.

On the other hand, we observed -- We weren't able to detect it using other antibodies, and it is known from model protein studies that, after sodium hypochlorite treatment, you are unable to detect them by either Coomassie, silver or auro dye. So very sensitive stainings, even if you have larger amount of proteins that usually should be seen.

Now it is also known that sodium hypochlorite fragments, protein bumps, by chloramine and nitrogen centered radicals, published by Hawkins and Davies in 1998. You have seen this slide, and this was an experiment described yesterday by Bob Rohwer with sodium hypochlorite. You also can see that infectivity disappears with that sodium hypochlorite, with a higher content of brain homogenate but also an extremely higher concentration of sodium hypochlorite.

From these studies it is known that with hypochlorite, the ratio of hypochlorite to protein plays a very important role.

Next slide, please. Summarizing the hypochlorite and sodium hydroxide, if you go back to literature, you can always find that at 0.1 normal you also got decrease in infectivity, be it with scrapie or with CJD or with hypochlorite, as we have already seen.

So if the PrPres or the proteinase K resistant part correlates with the infectivity, we could use these Western blots as an indication for activity of these agents.

The next slide, please. We also looked at stainless steel. This was an experiment performed by Aventis where they used stainless steel coupons incubated with hamster brain. Then they were either incubated in sodium hydroxide or purified water for injection as a control, and then washed. They recovered PrP scrapie by swabbing, analyzed the swab for PrP scrapie by -- I think they used a CDI assay upon recovery.

What they observed as, after sodium hydroxide treatment, again 0.1 normal, a significant reduction down to detection limit with their assay.

The next slide shows a very similar result, only dealing with somewhat larger surfaces, and a way to increase surfaces and still be able to

analyze large surfaces we used iron powder which allowed us to apply about the equivalent of 50 square centimeters onto one single lane on the Western blot.

What you see here, if iron powder was incubated with brain homogenate 0.1 percent final concentration, treated at neutral, washed with PBS and by vortexing we were able to detect the PrP scrapie and also proteinase K resistant fraction.

At time zero of 100 millimole incubation, protein was still on the surface; whereas, after 15 minutes we were unable to detect any proteinase K resistant prion protein on the surface. The way it was done, the iron powder was directly boiled in SDS loading buffer and then applied to the gels.

Next slide, please. We have seen it right before. It's the experiments that were performed. It also showed the sodium hydroxide treatment, again tenfold higher concentration, but in infectivity experiments infectivity was eliminated.

Next slide, please. It is not only steel surfaces that we are dealing with but also chromatographic resins. This was an experiment that was done by Aventis where they looked at DEAE-sepharose.

They incubated in a batch way DEAE-

sepharose where it is brain homogenate, washed either with water for injection or sodium hydroxide, then solubilized or recovered the prion protein by incubating with guanidine and hydrochloride, performed sealed dilution of this resin supernatant, and detected the prion protein PrPres or PrPsc using CDI or the ELISA.

You can see that they were able to detect proteins. However, after treatment with 0.1 normal sodium hydroxide they were down at the detection limit and couldn't recover any PrP with proteinase K resistant form.

Next slide, please. I am at the end. In conclusion, from these experiments we can say that sodium hydroxide and sodium hypochlorite treatment -- they both destroy the PrPres resistant form, proteinase K resistant form. Kinetics showed an extremely destruction of this proteinase K resistant form, even at low concentrations of sodium hydroxide like 0.1 or .05 molar and 100 ppm of active chloride.

Using Western blot techniques or CDI, we were able to show reduction of PrP resistant form in the range of up to 4.5 log, and these results are in agreement with many single point measurements based on infectivity data.

I thank you for your attention.

CHAIRPERSON PRIOLA: Thank you, Dr. Kempf. Are there any questions from the Committee?

I have one which, I think, you alluded to in an early slide. That is, your assay for PrPres by Western blot is based primarily on the three or four antibody. You mentioned that you checked different antibodies in one of the earlier experiments, the sodium hypochlorite.

Did you check antibodies in the central and C-terminal part of the molecule, the point being that you might not be completely destroying the res. but since you are putting it into sodium hydroxide and following it by protease K digestion, you are just chewing further into the molecule but not completely destroying it, and you are losing your epitope, your detectable epitope? Could you go to the microphone, please so they can record it.

DR. KEMPF: I could not give you right now which antibodies we used. I don't know it by heart, but it covered the range of the protein, the epitopes, and we also had some antibodies where we don't know where the epitope is yet, that we received from Australia, and they are not well characterized yet.

CHAIRPERSON PRIOLA: And when you gave

your log reductions, was that based on taking the same material and doing the titration in hamsters or was that based on your standard --

DR. KEMPF: That's based on the dilution of the Western blot assay. So normally you can detect about -- you have a dynamic range of 4 to 5 log in the Western blot assay, and in the CDI I don't know exactly. I would have to --

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: A question not specifically for Dr. Kempf, for anybody.

I can imagine that normal protein binds to a surface just like the infectious agent here. We don't have a good way to find it, but I can imagine that it may be there. Now suppose we have a surface with some infective agent on it, keep it wet.

Is there any reason to think that the infectious agent might spread into normal tissue around it? Did the problem get worse with time if you keep things damp?

DR. PETTEWAY: Let me see if I can maybe -- just from the perspective of, say, manufacturing process, and stainless steel are containers that are utilized. Keeping the surface wet, there probably is little for the infectivity to spread to. It's not

like the experiments that Dr. Weissmann described where there is intimate contact with living cells that allow the propagation.

That doesn't exist during this form of processing. So I think that a comment would be, there would not be -- We would not expect spread, if I understand your question.

DR. BAILAR: That wasn't the answer I wanted to hear, but --

CHAIRPERSON PRIOLA: Dr. Weissmann, would you like to make a comment?

DR. WEISSMANN: I guess I would just like to make the comment that, although PrP scrapie is a diagnostically reliable symptom of disease, it is not totally clear that infectivity resides in PrP scrapie as it is described as a protease resistant molecule. I'm just not convinced that this need be the case.

CHAIRPERSON PRIOLA: So that gets at the point of using PrPsc as a surrogate marker for infectivity.

DR. WEISSMANN: And I guess the other thing is I think one of the questions one has to ask is whether the resistance of the infectious agent, whatever it may be, is the same when it is absorbed to a surface as when it is free in solution.

CHAIRPERSON PRIOLA: Dr. Rohwer, would you like to make a comment?

DR. ROHWER: I find Dr. Bailar's question very provocative in light of the PNCA assay of Dr. Claudio Soto. This is a case where at least at the level of operationally, a P-K resistant PrPres resistant signal, this can be propagated in vitro with alarming ease, with or without sonication.

It works much less efficiently without sonication, but we have been able to reproduce this in the laboratory, and it's simply a matter of transferring an infected brain homogenate into uninfected brain homogenate, and you can actually increase -- The Western blot signal will increase over time, not very efficiently. It takes a while, but it gets to this question.

So the real -- and also to Dr. Weissmann's comment, are we increased infectivity at the same time that we are apparently seeing some sort of in vitro amyloidosis occurring in this transfer? We are looking at that directly.

We have a rather large experiment in collaboration with Soto using what we call limiting dilution titration, which is a pouisson titration of the type that you are talking about, to get an

accurate measurement, a sensitive accurate measurement of whether we are actually increasing the amount of infectivity at the same time -- in the same proportion to which we are increasing this Western blot signal. But I think it does -- The fact that this phenomenon has been described and that it is so easily reproduced says that we should be concerned about this at least until it's resolved, whether infectivity is involved or not in this phenomenon.

CHAIRPERSON PRIOLA: Thank you very much, Dr. Kempf.

I think we will move on -- Well, that's the end of our general background for Topics 3 and 4. That took a day and a half. Now we are going to be presented with Topic 3. Ms. Lillian Gill is going to go through Topic 3 for us.

MS. GILL: Good morning, and welcome to our Committee. Welcome to all of the participants in the audience.

I am Lillian Gill, the Senior Associate Director from the Center for Devices and Radiological Health, and I am pleased with some of the discussion we've heard this morning, and I think it is particularly pertinent to some of the excellent questions and responses we have heard to some of the

concerns that the Center has today.

Next slide. This morning our agenda focuses on the decontamination of products that come under the jurisdiction of CDRH. We are most concerned about the decontamination of these products, and we have a large responsibility.

Just to give you a bit of information on CDRH, our mission is to promote and protect the public health. We do that through ensuring that medical products that come onto the market are safe and effective, and we also have a responsibility for reducing any unnecessary exposure from medical, occupational, and consumer products from devices that -- and products that emit radiation.

We carry out that responsibility in five major ways, as you can see. We evaluate product before it goes on the market. We evaluate the performance of those products once it is in the marketplace through various surveillance mechanisms.

We have a laboratory science organization that is involved in some of its own research, looking at methods and product and the impact of some of these methods on the devices we regulate.

We participate in audits and inspections of product in the manufacture of those products and

looking at the validation of methods and in the validation of manufacture. Most importantly, we do quite a bit of communication with the industry, with health care professionals, with academia, and others. That is how we carry out our mission.

Next slide, please. While we are responsible for a vast array of devices from large medical systems to in vitro diagnostic devices, our focus for today and products under major consideration fall into three categories: Those specific products that come in contact with human tissue, and our interest today, is specifically neurological medical devices, the cranial drills, the implantables, electrodes, biopsy needles and endoscopes.

Next slide. We are also interested in some medical devices and products for general indication. These are the surgical instruments, medical suction tips, biopsy forceps, and products of that nature.

Our third category -- next slide, please -- that we are interested in hearing about are the medical devices used for sterilizing these products. These are your dry and steam sterilizers, the liquid chemical sterilants used in some of these systems and independent of systems, as well as the sterilization

accessory trays.

Next slide. With those areas in mind, our Center is particularly interested in hearing the discussions which relate to decontamination of products, and we hope to learn today what the published data can -- what published data can be used to develop methods for decontamination.

We hope to hear from you and learn from the discussions what the limitations are in using this data in the development of procedures. We are interested in the discussion of methods that can assure us of the sterility of medical devices, particularly regarding the bacteria and viruses, and we also hope to learn which of these approaches we can use in designing and interpreting TSE studies -- TSE inactivation studies.

To help facilitate that discussion, our Center staff is going to present to you some background information as well as provide some specific questions for your consideration and discussion.

Again, welcome, and thank you from CDRH for helping us with this challenging issue. Thank you.

CHAIRPERSON PRIOLA: Thank you, Ms. Gill.

Dr. Martha O'Lone will now present the background material for this.

CDR. O'LONE: Good morning. I am Martha O'Lone. I am not a doctor. I am a Commander in the Public Health Service. I am also a nurse, and I have 20 years experience as a neuroscience nurse, but currently I am a medical device reviewer in the Office of Device Evaluation, Infection Control Devices Branch.

Next slide. These are the objectives that I have for this morning: Basically, to provide background on sterilization validation for medical devices, and then, hopefully, to obtain some panel guidance on how to design and interpret sterilization validation studies for medical devices after exposure to TSE material.

Next slide. These are the basic questions that we hope the panel will be able to provide some help with this morning.

For prion contaminated critical medical devices: What is the acceptable sterilization process for prion removal and inactivation? What endpoint is appropriate? Is Log reduction of infectivity appropriate? Is there an indicator agent for prions?

Next slide. I will be covering the

following items in my presentation: Spaulding classification of medical devices, which I know we talked a little bit about yesterday; sterilization methods; medical device reprocessing steps; health care sterilization processes; medical device reprocessing review; validation; and then the available recommendations and guidances that we have.

Next slide. The science behind instrument classification has been described by Dr. Spaulding and was reviewed yesterday in our discussion as well. The Spaulding instrument classification is based on risk of infection and the area of the body where it is being used.

This classification is used in medical device reviews to determine if devices should be subject to sterilization or high level disinfection before use, depending on the area where the device will contact, as shown here. The medical device, a product classification that the FDA uses, aligns with the Spaulding classification.

Critical devices are the devices that normally enter sterile body tissue, as we have talked about before. Surgical instruments such as scalpels, neural burrs, are an example of devices that would be subject to sterilization prior to use.

Most of this presentation will center on critical devices because a primary area of concern for CJD such as brain tissue are considered sterile body tissue. When medical devices are used, they are reused, as determined by their design and materials, but most heavily by the ability to validate that these devices can be reprocessed.

Next slide. This is also not a new slide. After considering the Spaulding classification and medical device sterilization validation reviews, the potential level of resistance of the infectious organism is considered, and this order of resistance provides additional information that should be considered when determining the resistance to reprocessing and the level of resistance that should be validated for a review of a medical device that is to be reprocessed for multiple use.

We did discuss yesterday that bacterial spores are considered the most resistant microorganisms and that prions are thought to be of higher resistance than spores. What this slide does not emphasize is that the level of resistance does depend on the rigor of each of the medical device reprocessing steps, especially the sterilization method applied to each of the items in this descending

order.

Next slide. Our goal is to learn about inactivation of prions. The steps for medical device reprocessing may indicate -- may include, excuse me, the items in both cleaning, high level disinfection and/or sterilization.

Cleaning is crucial for subsequent reprocessing. The goal is to reduce bioburden by removal of organic and inorganic clinical contamination. Next is high level disinfection and, although high level disinfection is mentioned, the focus again is still for this discussion on critical devices which would be reprocessed after exposure to potential or known CJD.

Sterilization for critical device reprocessing is defined by AAMI, the Association for Advancement of Medical Instrumentation, as a validated process used to render a product free of all forms of viable microorganisms.

Currently, the sterilization endpoint is to kill spores, but as the previous slide showed, resistance to prions is thought to be higher than spores.

Next slide. The use of the sterilization processes that are used in health care settings to

reprocess medical devices that are currently on the market and available to the user -- The FDA has reviewed devices according to these methods. Also as Ms. Gill explained, we also review sterilizers for steam and dry heat as medical devices as well.

I want to bring your attention again to steam or moist heat sterilization as the most common method for prion deactivation and removal. It is also the most common method for sterilization of medical devices.

For gravity displacement cycles, steam is used at a temperature of 121 degrees Centigrade for 20-30 minutes. The pre-vacuum cycles use steam temperatures of 132-134 degrees Centigrade for three to five minutes.

It is important to remember that in the U.S. these sterilization cycles are fixed in health care, and it is rare for the health care user to reprogram the sterilizers. This would be significant when discussing recommendation for reprocessing devices that are contaminated or potentially contaminated with CJD.

Next slide, please. If the manufacturer wants to label their product reusable, FDA will ask the manufacturer to follow items in the FDA 1996

Reusable Label Guidance.

This guidance recommends clear instructions to the user, so that the user can properly follow the manufacturer's recommendations. Instructions must include appropriate microbicidal processes for the device, and these reprocessing steps must be feasible. For example, users don't have access to radiation. So that is not a viable method. It may be an over-example. The reprocessing instructions must be validated.

Next slide. As has been stated, for medical device reprocessing the sterilization process should demonstrate a spore (BI) kill to achieve a sterility assurance level of 1 x 10-6 or a 12 Log kill as its endpoint for conventional critical medical devices.

For medical devices exposed to potential or known CJD, the current approach to sterilization validation for medical device reprocessing with spores does not provide information that can be applied to removal or inactivation of prion.

Next slide, please. These questions remain for prion contaminated critical medical devices: What are acceptable sterilization processes for prion removal/inactivation? What endpoint is

appropriate? Can Log reduction be applied to determine safe use of a medical device and prevent transmission of prion infectivity? What indicator agent similar to the use of spores should be used for safe validation of sterilization of prion contaminated medical devices? Can prion contaminated medical devices and the equipment used in reprocessing in health care facilities be safely used?

Next slide, please. CDRH requires a virus validation study for some medical devices that incorporate animal derived tissue. Since virus validation studies for the medical devices with animal derived tissues were discussed at this panel's June 2002 meeting, I will not cover it in detail.

For medical devices incorporating animal derived tissue, the objective is a final product that is below one infectious particle per 106 devices. This is similar to a SAL level of 1 x 10-6 in traditional sterilization processes.

In the case of bacterial fungi, there are published methods by the FDA, but for virus validation there are published standards but no accepted methods. Virus validation is a step by step evaluation of an overall inactivation processes that is carried out in a controlled manufacturing setting, while the

sterilization of reusable critical medical devices is performed in health care settings.

Next slide, please. With bacterial inactivation or traditional sterilization validation of medical devices, it is a full scale sterilization process. These are the highlights for virus validation.

Virus validation is a model or scaled down approach with different steps in the manufacturing process to inactivate the virus. Then the steps are summarized for a total inactivation process.

Next slide, please. I want to conclude by providing information for current recommendations available for device reprocessing after exposure to CJD. Yesterday Dr. Taylor presented the WHO recommendations for reprocessing CJD contaminated medical devices.

The WHO recommendations begin with incineration for disposable instruments and those exposed to high infectivity tissues such as brain. One of the most stringent methods is listed on this slide.

For heat resistant instruments, immerse in 1N sodium hydroxide, heat in a gravity displacement autoclave at 121 degrees C for 30 minutes or 132

degrees C for 3-5 minutes. Rinse in water, and then the routine sterilization process.

Yesterday Dr. Brown, Dr. Stan Brown, mentioned his findings and recommendations on device material compatibility with reprocessing in sodium hydroxide and sodium hypochlorite. These findings included the potential for damage or residue on the medical device materials tested.

These recommendations do not include information about the unique challenges in device reprocessing, such as design materials and the intended use. These recommendations also do not provide an endpoint or indicator for the heat resistant instruments, nor do they address a validation method.

Next slide, please. Recently CDC's HICPAC, the Health Care Infection Control Practice Advisory Committee, has also been finalizing their draft recommendations for CJD contaminated devices. These guidelines are not final.

This slide addresses the recommendations for critical or semi-critical medical devices exposed to high risk tissues and/or high risk patients. They do provide some different information in Option Number 3 or numbered 3, to clean thoroughly, then autoclave

at 134 degrees C for 18 minutes in a pre-vacuum sterilizer or 132 degrees C for one hour in a gravity displacement sterilizer.

Option Number 3 does incorporate clearly the concerns about the importance of cleaning. The HICPAC guidelines do begin to address other concerns in the last point on the slide, especially discard contaminated medical devices that are impossible or difficult to clean.

That concludes the information I have at this time, and hopefully, it will give you enough background to continue with discussion and follow-up with the questions that will be provided by Dr. Durfor later. Thank you very much.

CHAIRPERSON PRIOLA: Questions for Commander O'Lone? Dr. Bailar?

DR. BAILAR: A little simple mathematics: I assume that you would like for this standard of one infectious particle per 106 maximum to apply to any prion disease as well as to anything else.

What is the prevalence of CJD or maybe the prevalence of any prion disease in an asymptomatic stage in the U.S. population likely to come to surgery? I would guess that the prevalence is something higher than one in 106.

CDR. O'LONE: What is the prevalence of?

DR. BAILAR: The prevalence of asymptomatic CJD or other prion disease?

CDR. O'LONE: Well, to the best that I can understand from reading about the epidemiology of CJD, that number is unknown. I don't know if someone has some better information that they could answer with that.

DR. BAILAR: I wouldn't expect a precise answer, but if the risk is greater -- If the prevalence is greater than 1 in a million, then your chance of hitting that 10-6 risk with a single exposure is going to exceed your guideline.

CDR. O'LONE: Well, first I have to say that I don't know if 10-6 is appropriate for CJD infectivity. I don't know enough about that. I'm not sure that that is clear either. I understand what you are saying otherwise about the mathematics, and we certainly do want to make sure that the reuse of medical devices is safe.

CHAIRPERSON PRIOLA: I think, Dr. Bailar, there are a couple of people over here who might be able to address that more directly. Dr. Schoneburg, do you want to --

DR. SCHONEBURG: Hello. In the United

States at CDC we get about one case per million population per year. So there's what, 284 million people or so. We get about 284 cases every year reported to us.

Now that's incidence. That's why I'll just give you some numbers to play with. What we don't know is -- What that comes out to, by the way, is about one out of every 9,000 or 10,000 people in the United States dies from CJD, because this incidence has been stable for -- well, since 1979, since we have had that data. If that continues to be stable like that, you can look at a list of all the deaths in the United States, and one out of 9,000 or one out of 10,000 of those will say CJD. Okay?

Now how long is the period of infectivity? That's what we don't really know. Okay? So maybe each of those individuals who I am counting as a case were infectious for ten years. I know that Paul Brown at one time when he was trying to calculate risks for blood used about a ten-year period.

Then the other issue to raise is that, even though I say one per million per year, there is a very distinct age related difference in the incidence. There is practically nobody in the United States that gets sick with CJD who is a teenager and,

certainly, very few cases under 30 years of age. After 55 years of age, however, the incidence goes up quite markedly, peaking at around 68 years, and then -- - 68-70 years, and then comes down again.

Now people, of course, die from other diseases as time goes on, and how many of those individuals might be infectious because they hadn't had the opportunity to die from CJD yet, we don't know. But these are some numbers. You would have to fool with those to get some idea of what the odds might be of an individual coming to a hospital who would be infectious and still not symptomatic.

The age distribution would be a clear risk factor. In other words, a child who came in for surgery -- extremely unlikely, probably wouldn't even consider that that person would be positive. As you get into the older population, the risk would be much higher. But again, we are talking about a relatively rare disease in the United States.

CHAIRPERSON PRIOLA: Dr. Durfor?

DR. DURFOR: Charles Durfor, Center for Devices at FDA. I wanted to address one of the other questions you raised, which was the issue of one infectious particle in 106 products. That is a value that has found great use in terms of viral safety.

The issue of what is an acceptable risk for TSE products is one we bring before this Committee today. So I don't think you can make that assumption at this time, what that value would be, but instead it's one of the questions we are going to ask this panel to give us guidance on.

CHAIRPERSON PRIOLA: Dr. Edmiston?

DR. EDMISTON: This has been an interesting discussion, because we've had a number of both pragmatic and mechanistic discussions concerning this issue. But let me talk about where the tires hit the road.

It may be impossible to define a threshold in this particular scenario, for a number of reasons that have actually been alluded to by members of this panel and also by several of the distinguished individuals who have presented data here. I think, however, it is important to recognize there are some parallels here.

One of the parallels has to do with antibiotic resistance in this country. If you look at how antibiotics are being used in this country, you look at antibiotic formularies. You could have the most restricted antibiotic formulary in the country, but if your infection control practices are abysmal,

you are still going to have significant problems with resistance within hospitalized patient populations.

What I would like to point out is, if you look at the incidence that we have seen of CJD, especially in health care workers since 1976, one could make a strong argument that it's been our infection control practices within these institutions which have contributed to the low incidence that we have seen over the past 20-25 years prior to 1975 or prior to 1970.

So I think the issue at hand is very simple. We have to recognize that, while we can discuss the possibility of designing assays and studies that will give us a level of confidence, we can't forget that this is an adjunctive process in parallel with our infection control practices.

I think that's very, very important to realize. Dr. Rohwer, I think, you are greatly concerned by some of our methodologies within institutions in light of our inactivation studies. But I can assure you that the FDA is charged with protecting the health and wellbeing of the general public at large. That's what my responsibility is at Frederick Hospital for the patients and the staff members in that institution. So we take this all very

seriously.

So I think it's important to realize this is a two-tiered process. Not only are we trying to define validation studies and processes that can reduce the risk, but there are already procedures -- policies and procedures in place which fall outside of that, which are doing the same.

CHAIRPERSON PRIOLA: Dr. Bailar.

DR. BAILAR: I think what I'm hearing is that a single exposure to an apparently healthy American of past childhood and early adulthood, the way these things stick to hard surfaces, would result in a risk of more than one in 106, but maybe that isn't the right standard to use here. Is that a fair summary?

CHAIRPERSON PRIOLA: I'm not sure that I understand the question. Exposure of an individual of any age group to TSE contamination -- is that what you are referring to? That's different.

DR. BAILAR: No. Exposure of an instrument to an average person off the street who has no evidence of disease might result in prion contamination, CJD contamination, of that instrument because the disease has not progressed to the stage of being identifiable, and that the risk of that is

perhaps greater than one in 106 -- 10-6.

CHAIRPERSON PRIOLA: Okay. I don't know your name.

DR. LIN: My name is Chu Lin. I'm the Vice Chair for Device Branch in the CDRH.

I think that the question that Martha O'Lone present when she mentioned about particularly when you talk about stuff like this and is the sterility assurance never over 10-6 -- that is not what we are talking about. This is the endpoint that we said is one out of 1 million device would allow for nonsterile. That's what the concept of SAL 10-6 is talk about. Okay?

That is sort of a accepted part in the validation field, important medical device, because there is no way you can sterilize devices completely, so called sterile, just like pharmaceutical industries. So that's why you use that concept of sterility assurance label 10-6.

When you talk about diseases, talk about -- when you have a reusable device manufacturer come to FDA, said I wanted to report the use of a device or, by the same matter, for the industrial or the manufacturer said I can sterilize this medical device. This is the endpoint that we use to decide whether the

device is sterile or not.

I don't know whether that answers your question.

CHAIRPERSON PRIOLA: I think part of what Dr. Schoneburg, I think, was getting at is that that risk that you are discussing, this one in a million, since the distribution of CJD in the normal population is a bell shaped curve with an average highest incidence at, you know, 55-60 years old, that's the population where you would be most concerned of that carryover of that contamination, not -- and it's an increasing level of risk with age, and a decreasing level of risk after, apparently, the age of 60.

Is that more what you are getting at?

DR. FREAS: Microphone, please. That's getting at it, but that may be an age range where neurosurgical procedures are more common than in the rest of the population, too.

What I'd really like to know, and I don't think anybody can answer it, is what is the risk of a reusable device being used in an apparently healthy person on the table coming away contaminated with one of these prion diseases?

DR. HELLMAN; I don't know that I can answer that question. Kiki Hellman, FDA. But I think

we straightened out the incidence question, the one 106, and then Larry's comment that about one in 9-10,000 of the U.S. population. That would translate to that.

I think the concern in a hospital and a surgical setting is to consider the risk of age distribution, since certainly, anyone that comes into the hospital age 55 or over for a surgical procedure would be the -- perhaps incubating the agent.

The concern then needs to be with any instruments that are used in that age population to take special care with those instruments, not on children that come in at 10 or 11 or 12 for tonsillectomy, for example. There may be older individuals that come in for a tonsillectomy. You would be concerned about those instruments.

So considering the incidence of CJD in the U.S. population, what that translates to -- the older individuals coming into the hospital for surgical procedure, those instruments that would be used on that age range population. Does that help a little?

DR. BAILAR; It does help, though I don't think I would want to move to a system where we have instruments segregated by -- for use in different age groups.

DR. HELLMAN: Oh, no. No, no, no. But I'm just trying to delimit it for you.

DR. BAILAR: Thank you.

CHAIRPERSON PRIOLA: Dr. Hogan.

DR. HOGAN: Maybe I can provide some numbers. We actually looked at the issue of prevalence when we were trying to calculate risk for corneal transplantation. This is Dr. Bob Kinnean and myself. If you use the assumption -- and many people in the audience know about this. If you use the assumption of 10-year incubation with six months of clinical disease prior to death, then the prevalence of symptomatic -- nonsymptomatic patients in the United States would be about 2,600 per year per -- 2,600 per year in the United States period.

That's using the data on incidence of CJD in various age groups. You can break that down to around 460 in the age group between 60 and 65 a being the highest incidence. Those numbers are published. But I think a more important issue here, based on your question, is how many transmissions have we had in the United States with neurosurgical instruments using current methods? As far as I know, it's zero. Can someone correct me?

DR. EDMISTON: And I think that relates to

our infection control efforts in being able to identify patients such as patients in specific risk groups. That's an important component that we can't forget, the ability to be able to identify patients.

One of the things that we don't have with CJD patients is an early warning system for these patients. So we have to use criteria that are very broad. Quite often, we'll be sending specimens out in patients who have died at post mortem, and at post mortem evaluation it's been determined that they have had CJD. That's the issue that you are most concerned with right there. That's that population that we are trying to address.

Our neurosurgical colleagues are pretty attuned to this, and they pretty attuned to it in the point that they are looking at alternatives in terms of managing a number of these age populations, and especially in doing brain biopsies, as indicated yesterday. There's more and more neurosurgeons that are moving toward the use of disposable hollow bore devices, disposable biopsy needles.

I think that's an issue that is extremely important, and that falls into that infection control arena. So while I may not be able to put an endpoint, especially in the decontamination phase, I think we

have to recognize that there are other mechanisms in place which are trying to get to the same point.

CHAIRPERSON PRIOLA: Okay, thank you, Commander O'Lone, for your presentation. I think that leads us, if there are no more questions, to the public hearing portion.

DR. FREAS: As a result of this meeting announcement, I have received three requests to speak in the open public hearing. FDA has reviewed these requests and, because of the scientific nature of these requests, we are giving each of the next three presenters ten minutes to make their presentation.

I will call them to the microphone in the order in which I received their request, but if they have decided amongst themselves a different order, please let us know before you start speaking.

The first speaker I have, based on order of request, is Dr. Gerald McDonnell, Senior Director of Technical Affairs at STERIS Corporation.

DR. McDONNELL: I am actually going to go second today. I am going to let Dr. Burke from AdvaMed give some comments first, and then I will go through some technical stuff.

DR. FREAS: Okay. Our first speaker, Dr. Peter Burke from AdvaMed.

DR. BURKE: Good morning. My name is Dr. Peter Burke. I am the Senior Vice President, Chief Technology Officer for STERIS Corporation. I am here today to be the spokesman for Advanced Medical Technology Association, more commonly known as AdvaMed.

AdvaMed is the largest medical technology association in the world, representing more than 1100 innovators and manufacturers of medical devices, diagnostic products, and medical information systems. Many of these products are manufactured from materials derived from ruminants that can be sourced from countries outside the United States. Thus, the potential risk of TSE contamination associated with medical devices is an important issue for AdvaMed member companies.

In fact, manufacturers consider source control to be the most effective safety control measure available to mitigate any potential risk of TSE introduction. AdvaMed members made a recommendation to FDA last year that the agency adopt a flexible approach to allow device manufacturers to determine measures of theoretical risks for medical devices.

Source control was the central pillar of

that flexible approach, and we believe that this is a highly effective step in preventing the contamination of medical devices and, as importantly, manufacturing facilities. However, in order to prepare for any potential risk of TSE contamination, this committee, CDC, FDA and USDA all face the monumental task of developing criteria for designing and validating -- most importantly, validating studies intended to evaluate the effectiveness of TSE decontamination methods.

We commend this effort, and we believe that it is necessary to ensure the continued availability of safely reprocessed medical devices and also medical devices containing animal derived materials in an environment where the number of TSE-free countries is declining, and can change overnight.

In the United States there are currently no approved guidelines for decontaminating medical devices that might potentially be contaminated with prions, considered the causative agent of TSEs. Prions are, as we have heard for the last couple of days, highly resistant to the routine methods of decontamination and sterilization currently accepted for medical device processing. The removal of prions presents a significant challenge to the manufacturers.

I will break up my comments into general decontamination and device control as well.

The challenge of decontaminating medical devices and manufacturing facilities that may be potentially contaminated with prions has several components, and it is important to consider the body of experimental work that has been done.

To date, in experimental studies, no single decontamination method has been shown to be 100 percent effective against prions. Therefore, a combination of methods is generally recommended.

Current decontamination methods are based on recommendations from the World Health Organization or WHO. WHO recommendations are based on a review of the current published literature. The effectiveness of these methods is difficult to assess. There are no standardized methods to evaluate the effectiveness of any given decontamination procedure for prions.

Based on our review of the literature used by WHO, it is difficult to determine which decontamination methods are truly effective. It is also difficult to compare studies, as a variety of prion proteins, such as scrapie, BSE or CJD, were used.

In addition, the studies employed

different preparation methods, purified, nonpurified, homogenates or intact brain, and used different test methods, some being suspension, others being on hard surfaces, carriers.

Evaluation of decontamination methods also failed to consider the antimicrobial effects of biocides and physical/biological processes, which may vary based on the process parameters -- in other words, active concentration and temperature. Consequently, the results of many studies cited in the literature may not be reproducible.

In the United States, the Healthcare Infection Control and Practices Advisory Committee known as HICPAC of the Center for Disease Control & Prevention developed draft guidelines as part of their Guidance for Disinfection and Sterilization in Healthcare Facilities. These guidelines, which are yet to be approved, are also based on WHO recommendations. AS a result, they, too, fail to include a standardized method of evaluation.

If we are to answer the question of which method should be employed, we must first have a mechanism to compare the available methods. In addition, the panel must recognize that, in the current absence of globally accepted standard methods

for evaluation, additional studies would likely be necessary to achieve more definitive global guidelines. We believe that today's proceedings are an important first step to do so.

Currently, contamination of manufacturing facilities is a theoretical risk. If the products were to be contaminated with TSE agents, the decontamination of manufacturing facilities, in order to limit the potential for cross-contamination of medical devices or other regulated products, presents major problems for manufacturers, with a considerable logistical challenge.

Since to date no single method of decontamination has been proven 100 percent effective against prions, any FDA requirements to decontaminate manufacturing equipment and facilities should take into consideration the potential risk of cross-contamination from contaminated materials and the potential for transmission of TSEs based on patient or user contact. Decontamination methods should be based on this risk assessment and whether the process selected has been established as being effective under the specific use conditions.

If effective methods are identified, other considerations would come into play. For example,

would the method be compatible with the medical device production and manufacturing equipment? It's an interesting question.

Another question would be identified decontamination methods should be compatible with surfaces being treated to minimize damage to manufacturing equipment. How frequently should one apply such methods following each manufacturing run, after each single lot or at some other determined frequency? So there is an issue of frequency here.

How does the implementation of prion decontamination methods impact equipment qualifications and processes from a validation perspective? Again, will it be necessary to requalify all manufacturing lines?

The answers to these questions are important, as they will impact the day to day manufacturing of medical devices, which are so critical to health care today. There is the potential that any new and possibly onerous requirements on medical technology manufacturers could limit manufacturers' ability to provide needed quantities of life saving medical products in a timely way to the patients who need them.

AdvaMed strongly encourages that any

discussion about development of standardized decontamination methods to reduce any potential risk of BSE cross-contamination take these considerations into account.

Furthermore, it may be appropriate to consider alternative approaches for those medical technologies that do not come in contact with human or animal contact. Material control for these products through the use of standard quality systems must not be overlooked as an alternative approach to the implementation of any new decontamination procedures.

Material control processes for these products already address the identity, traceability, handling, and disposal of materials within their quality systems. Assurances provided by these systems provide a viable alternative to facility decontamination.

Let's look at device issues. Another component of the decontamination challenge is the impact of various decontamination methods on a device. Can that device withstand being subjected to new and potentially rigorous decontamination and processes, above and beyond the current regimen of safe and normal sterility practices, and still retain performance integrity to remain safe and effective for its intended use? The answer is, obviously, very

complex.

Several of the current WHO recommendations for medical device reprocessing will cause severe damage to common medical device surfaces. I think we've seen some of those in the presentations already.

For example, WHO's recommendation for using 1 N NaOH can severely damage aluminum and stainless steel components when used in an autoclave, and even the autoclave could be damaged from the internal chamber perspective.

The impact of current decontamination processes on devices and in vitro diagnostics, known as IVDs, is unclear. IT is likely they would not stand up to these extreme decontamination practices.

Most IVDs contain some sort of animal derived materials, much of which is derived from ruminants. These materials are key to the performance of IVDs. In many cases, the materials have been developed to yield certain unique performance characteristics. If required, decontamination practices could literally destroy or inactivate this ingredient. IN that case, most IVDs would be ineffective.

Since these devices are not intended to contact either the human body or animals, requirements for decontamination procedures would be superfluous.

Where decontamination is a viable option, the method of decontamination is an important consideration. The method used must be comparable with the material of the device -- or compatible with the material of the device. When a combination of procedures is required to decontaminate a device, the effect that each one has individually and in combination must be answered.

The decontamination process must not render the device unsafe for its intended use. We encourage the Advisory Panel to take into account the unique concerns associated with the decontamination of medical devices whose original origin of design never contemplated cleaning and sterilization after exposure to potential TSE causative agents.

In conclusion, materials of animal origin provide countless functional and clinical benefits for treating many serious diseases and medical conditions. The potential risk for cross-contamination of surfaces form materials of animal origin or transmission of TSEs onto medical device applications requires the development of decontamination processes that are effective and compatible for their intended use.

AdvaMed stands ready to work with the CDC, FDA and USDA to ensure the availability of safe

lifesaving and life improving medical devices and technologies that can incorporate animal derived materials. However, we believe that any effort to develop a methodology to evaluate the effectiveness of methods for removing TSE contamination from medical devices must be done on a global stage.

Medical devices cross boundaries. They are worldwide. This effort must cross the same boundaries and pull together government agencies, manufacturers, researchers and other thought leaders from around the world.

AdvaMed strongly -- has already proposed to FDA that government and industry cosponsor a workshop on decontamination processes to obtain a clear picture of the state of the art for such practices. Such a workshop would allow for critical review of existing international guidelines for prion decontamination for practical application in the U.S., including the need for validation of proposed methods and compatibility with medical devices.

The workshop would establish support for a research agenda on prion decontamination, including efficacious testing methodology, confirmation of effectiveness of proposed processes. Lastly, a dedicated working group of stakeholders should be

established to work with FDA on this issue, and support development of policies and guidelines for safe and effective decontamination practices.

Thank you for considering our comments. Our members strongly support the efforts to develop a standardized methodology for assessing current and future decontamination procedures to reduce the potential risk of TSE contamination in medical devices and medical device manufacturing facilities. I thank you for this opportunity to speak to you.

DR. FREAS: Thank you for your presentation. Our next speaker will be Dr. Gerald McDonnell, Senior Director of Technical Affairs at STERIS Corporation.

DR. McDONNELL: Thank you very much for the opportunity to talk to you today. I am going to talk about decontamination of surfaces contaminated with prions. The background to this is that I work for STERIS Corporation, who are a leading supplier of infection control and surgical support products worldwide.

For that reason, we often get questions on how do we decontaminate surfaces against prions from, say, a medical device perspective or from a pharmaceutical or life sciences perspective, or even

from a research perspective in research labs. So this is, of course, of great interest to us.

Can I have the next slide, please. I think this has been well reviewed during the last few days. But, certainly, I think we can definitely say that human tissues and contaminated surfaces can transmit TSEs and, despite how rare these diseases are, we have actually seen clinical cases and they have also been shown experimentally.

I will use a reference from the paper that Dr. Weissmann spoke about earlier, that prions are readily and tightly bound to stainless steel surfaces and, I think you will agree, to other surfaces, based on his presentation this morning, and can transmit the disease to recipient mice after even short implant times.

Next slide, please. Now this slide looks familiar, because you have seen it before. A lot of us use it and I have even published this myself. But there is one important point I needed to make here.

Prions do demonstrate resistance to routine methods of decontamination and sterilization. But we often think of prions as being another microorganism.

So when we think about how do we kill

them, well, we keep increasing the temperature. We keep increasing the time. That may not necessarily be the case, because you ask a biochemist how he wants to kill a protein, it's a little bit different to the way he might kill a microorganism. I think that is a very important consideration.

Next slide, please. I'm going to take you through some of the questions that we have been asked and that we have asked ourselves when considering the current guidelines.

The first is cleaning. When I first looked at this, my question is, well, could I actually increase or decrease the risk by cleaning; because, yes, you do get physical removal from the surface, but then where does it go, or can it bind to other surfaces?

Because it is a lipophilic soil, in comparison to some of the results that Dr. Rutala presented yesterday, he showed you lots of data with aqueous soils, but these are not aqueous soils, and these are a lot more difficult to remove from the surface.

So when we think about cleaning with prion, we may need to make specific recommendations of what we mean, what types of products should be used in

that case. We have seen a lot more discussion on what actually happens then when they go down the sewer and into the sink and other things like that, which is, I think, getting more discussion in Europe right now.

There's also some recommendations that are actually not specific to the U.S. but I thought were worthwhile mentioning. In Germany, we had cases where aldehyde-based cleaners were used, which seems like a contradiction of terms, but it actually brings up an important point also, in that not only cleaners, but we also use disinfectants that do have cross-linking or fixing activity. I think we need to think about with recommendations whether they should be used or not in cases of high risk or in cases where TSEs are expected.

The use of alkaline cleaners has been recommended, because they are extremely good at removing proteins from surfaces, and they are a part of standard recommendations in countries like France and Germany.

Next slide, please. Steam sterilization: I think this has already been well looked at. But it is true that the data is conflicting, and it is not completely effective. I think this is one point where we do see a major difference between what we think

microbially and what we think biochemically, in that there is some very nice data that has been published by both Ernst and Race from Rocky Mountain Labs and from Taylor -- from David Taylor in Edinburgh that, as you increase the temperature, you can actually get more resistance. I think that is something that we need to consider also.

Next slide, please. Now here is another example with sodium hydroxide. This comes from a paper we published recently. That's device damage. Well, you can see the obvious effect of doing sodium hydroxide here with some devices in Canada, and I think you would all agree that you wouldn't be very happy to hand them over to a surgeon for use.

Sometimes it is not the damage that you can see. It's the damage that you cannot see. Generally speaking, over multiple cycles, we really do need to look at the effects of what that actually means. If a device was to break during a procedure due to damage, then that could actually be more dangerous than the actual decontamination against TSEs.

The safety concerns not only apply to the device but, of course, they also apply to the person that is doing the reprocessing. If you can imagine a

nurse that's trying to handle a tray of sodium hydroxide that is cold going in, potentially hot coming out, we need to be very particular about what we recommend from a safety point of view of handling, if we do recommend sodium hydroxide in a health care facility.

Next slide, please. So in summary, TSEs can be transferred to medical devices and other surfaces. Recommendation: Decontamination methods need to be verified to be priocidal compatible and safety, just like any other decontamination method that is currently regulated in this country.

Further, alternative decontamination technologies need to be looked at also. I think you have heard a lot about existing ones today, and I will try and point out some new ideas as we move on to the next slide.

What I'd like to do next is just to point out some data. This is where I get a little bit more excited. The decontamination research that I've been involved in includes two different things. There's test methodology development and trying to verify and validate that methodology as being practical, as well as then using that methodology to look at decontamination technologies, both existing and

developing.

Next slide, please. This method should be very familiar to you right now, and I think it is one of the best published methods that we have seen. We have also used this method and tried to optimize it in any way we can to make it more practical from a validation point of view.

It's a very simple method. This contamination or the preparation of a brain homogenate, contamination of stainless steel wires. I will mention something here of the sort of things we have looked at during validation.

We have looked at the amount of material that remains on the surface by using a homogenate or also by putting that instrument directly into the brain that's contaminated a number of times. The amount that we see by doing that inoculation or simulating surgical procedure compared to using a homogenate is the same, which we thought was important.

There's a drying step, and you can see me moving toward more of our worst case scenario here that I think is important. Then you can expose it to liquids or gases or steam or any other process. It gets inserted into a test animal, in most cases a

hamster in this case, but you can also use transgenic animals in this case, depending on the TSE in use or the PrP in use, and then incubation of the animals.

Next slide, please. Let me give you a typical study design, and this is a TSE strain. It's scrapie and going into Syrian hamsters, using stainless steel wires as the device. The test inoculum is 10 percent brain homogenate exposed for one hour, and then dried for 16 hours at room temperature.

There are 14 control groups, and this is what makes these experiments very large. There is a tremendous amount of controls. But in addition to the usual positive controls, which includes dilution of the material, there is also negative controls; and I have also done some wash-off controls as well to try and identify how easy it is for the protein to be removed, and then actually to look at decontamination methods to verify existing as well as developing ones.

Next slide, please. This is a typical curve of what we've seen with positive controls. While you've seen these sort of things before, like me, you are probably very -- I'm very interested in the top part of this graph to look at. This is, of course, mortality over serial dilutions, what actually

happens over that endpoint, and our animals are still under incubation at this time. But as far as we have incubated so far, we are no longer seeing infection after a 6 Log reduction.

Next slide, please. This is interesting. These are the results form the wash-off controls. I Think this does mirror what Dr. Weissmann said earlier on. What we have looked at here is just by doing rinses in PBS. What we have done is taken them a third dilution, a fifth dilution, and you see the mean mortality with a rinse or with no rinse.

I think you will agree that, at 280 days incubation or over nine months, there really is no difference. So I think that does verify that these proteins are very well attached to the surface afterward, which changes our perspective of what we would normally expect for protein removal from a surface that would normally be aqueous.

Next slide, please. Some autoclave studies: These were not a surprise to me, but may be a surprise to some of you. Now there is no cleaning in this case, but when I look up that porous load autoclave cycles of 134 for 18 minutes, you have approximately a 4 Log reduction. But if you take those same stainless steel wires and immerse them in

water and then put them into the autoclave, you get a greater than 6 Log reduction.

I think what actually is happening is that the protein during a porous load cycle can get shocked, and it basically collapses onto itself, which makes it more difficult to penetrate, while in water it allows it to loosen up and then lets the heat actually have its activity.

If you looked at just during what most people would do routinely in the hospital, an enzymatic cleaner followed by gravity drain cycle at 121 degrees, 20 minutes, you actually get a greater Log reduction than by the more aggressive 134 degrees for 18 minutes.

Next slide, please. Let's look at some cleaning studies. What sort of effects do we see with cleanings? From what I know, I think this is the first time that cleaning has actually been looked at in this assay.

If you look at a formulated cleaner, an enzymatic cleaner which has been formulated to be compatible in a medical device, its generally used formulation includes surfactants, enzymes, other things that makes it work very well. We are looking at approximately a 4 Log reduction. But we have also

managed to investigated alkaline cleaners which, I think, are becoming very interesting in that not only do we see a 6 Log reduction which can make sense, because you're getting a lot ore physical removal from the surface -- that's what these products are good at -- but it is also -- we are also showing that at low concentrations that they are actually breaking down the prion molecule, which I think is very important.

Next slide, please. Then some further technologies: We have investigated a phenolic disinfectant which had been previously published as being effective. It did show a 6 Log reduction on the surface. That wouldn't be for use in a medical device. It's more of a routine decontamination sort of product.

There is also a formulated oxidizing agent which we have tested, which gave approximately 4 Log reduction, and then an internal control of sodium hydroxide.

Next slide, please. I thought I would leave you with that, if you haven't seen it before. I think it reminds me to say that at the same time we have to remember that we have to keep guidelines practical for use in hospitals. I will ask you to remember the nurse in the hospital actually has to do

these things, and to make her life as easy as possible. Thank you very much.

DR. FREAS: Thank you, Dr. McDonnell. Our next speaker is Dr. Richard Marchand from the University of Montreal.

DR. MARCHAND: I am Richard Marchand. I am an associate professor in infectious disease at the University of Montreal, and I work in an affiliated University hospital. I also work as a consultant to different companies in the field of infections control, and here in this case it is TSO3, which takes care of my expenses for this visit. TSO3 stands for Technology Sterilization with Ozone.

Next, please. Now I want to show you the bullets of the take-out message I would like to give to the Committee, and at the same time give examples of the problems, why I plea here for a forum for the industry and a forum to discuss standards.

Fourteen months ago I received in my office the medical chief of my division in panic because there was a patient that came back to the hospital. He had been operated for heart surgery three months before, and came back with the signs of CJD, which was confirmed, and he died several weeks ago.

So, yes, it happens in institutions. It happens in hospitals where we have to deal with CJD cases or possible contamination. Now when you try to look at solutions and find solutions which are practical for hospitals, you want to find solutions for prion inactivations, and there is no definition of minimal performance requirements, no definition in terms of endpoint.

Is Log reduction, as said Ms. O'Lone, good? In fact, if it is not predictive of loss of infectivity, why would we do these things? There is also a lack of -- or a need for prion inactivation indicator. If we don't have minimum performance requirements, nobody can design an indicator that can measure, because there is no performance requirement to be measured.

If you want to evaluate new technologies, how can you do it if you don't have worst case scenarios which include or do not include washing techniques?

So as you heard this morning, prion inactivation can be looked at by many different ways than just the conventional way of living microorganisms to kill. If you look at prions, for instance, as slow acting carcinogens, because they are

not living, which can give a kind of brain cancer many months after a long period of incubation -- If you look at the slow toxin and you use that aspect to look at it, you will focus more on washing and cleaning techniques. You will focus more on molecules that can modify charges to prevent absorption on surface.

You will focus on passivation technologies for metals and plastics to prevent them from absorption, and you will look at cell lines, because you know that with toxins there is no zero cut in terms of infectivity or activity. There is no zero thing. You just go and decrease -- decreasing activity, and you accept the concept that the surface, like a metal, can act as a catalyst, as it does for polymers, and we are talking about molecules that behave, in a sense, like polymers here.

So next slide, please. Yes, I have been working with my colleagues at the University on fungal prions for over five years now. These molecules behave like prions, spontaneously polymerized beta leaflet are heat resistant. They are not infectious to humans, and we can modify by mutation to increase their resistance to heat, and they can be useful for process indicator. But actually, we cannot build them and make them,s because we don't know how much we do

we put in there. Is it to be inactivated in one hour, 30 minutes, two hours, six hours? There is no minimal performance requirement that tell us how to build them and give us goals, and we don't have any forum to discuss what could be a goal or a minimal requirement performance -- performance requirement for that thing.

Next, please. There are also new technologies that are in the pipeline. Ozone is one, but you have plasma glow discharge technology, some other plasma technologies, and some chemicals that are coming out.

These molecules have high redox potential, to the point they get oxidized material, including proteins up to CO2 and in reality, challenges by protein are much less than oil substance and lipids that can be done.

So when you want to tell these proteins which type of prions can be used, as you see, there are many strains. All of them behave differently. There is no guideline on one type of strain in particular, and where do you discuss again? To which firm do you address to find which one to test? Which animal do you use to test? Is it an animal that develops a disease like the human one or is it an animal that is highly sensitive? What do you

prioritize in terms of sterilization or inactivation, and what is to be measured, as we discuss again? Is it reduction of infectivity or reduction of protein mass or whatever?

Once again, we need a goal to measure. We need a forum to discuss that, because these are highly technical things to debate, because they vary form one technology to the other, one inactivation technology to the other.

Next, please. Now for new technology assessment, surface sterilization process which are in the pipeline and will be available very soon depends on clean instruments. Dr. Rutala showed us how it is important to clean, but what is properly clean?

I asked two years ago to my CSR staff to bring the best cleaned instruments they can find, and out of these 40 percent, under a binocular microscope, were capable of showing us presence of organic material. They were horrified about it, because they thought they were clean.

So visual inspection is not in a hospital system a very good marker of absence or presence of organic material. What is properly clean? I don't know. So how can we define a proper challenge if we do not include cleaning processes in the whole

process, because it is part of sterilization.

So we cannot just look at sterilization with a process sterile in itself, and that includes with these new processes the previous step, which is cleaning.

So we are back to the worst case scenario definition. What is a worst case scenario? What is plausible? Is it a chunk of brain put in a bottle or a soup, a chunky soup-like material extract that we put in a bottle for a surface process? It won't work. None of the actual surface processes will work.

So we are back to worst case scenario definition. It's needed to test, to evaluate a new technology. Next, please.

Why do we need these guidelines? Because these studies take years sometimes, if we wait years for the animal to develop a disease. They are very expensive, and actually the industry, to invest millions need a minimum of consensus, because they won't be able to claim performance, and they won't be able to sell with a claim.

So if the industry wants to -- and it wants to get involved with prion problems -- it needs guidelines. Next, please.

So I will put my university professor hat

here. I can say that, even three years ago, the industry was not ready, from my standpoint, to get involved in the prion inactivation proposal of standards. It is now. I believe it is, and if we can identify a forum where there is a lot of people there that can help us to agree on some definitions, agree on the worst case scenario problem, agree on a lot of thing -- and this cannot be left to the regulatory bodies alone, because all the instruments are so diverse that the industry must be involved right from the beginning, because each specific instrument can have different properties and different behavior in any type of sterilization.

So the industry must get involved, and we have no doubt about that. So if we can identify a forum which can be, for example, an international workshop as proposed by AdvaMed or anywhere else, and propose standards -- For instance, can we replace the sterility assurance level, which refers to a probability of an instrument being contaminated, by a safety assurance level, a probability of transmission of disease of one in a million?

Is this the concept that will have legal issues, because the definition of sterility is a legal definition, in a sense. But can we change some

concepts and agree on that, to give us guidelines and a work frame to develop new technologies.

We will have to live with the concepts of limited knowledge, best attempt, acceptable risks. As my colleague here said, acceptable risk is one here, because there is no zero risk with prions. We cannot -- It goes down -- The risk goes down with the exposition to the sterilant, but it won't be zero, never.

So what is an acceptable risk? If the risk to take your car back and forth from home to work every day on a yearly basis is one in 200,000, is a risk on one in a million acceptable for transmission of a disease? What is an acceptable risk in life, and can we do and develop technologies in accordance with that? Thank you very much.

DR. FREAS: Thank you, Dr. Marchand, for your comments. Is there anyone else in the audience who would like to address the Committee at this time? There will be another open public hearing after lunch today. Dr. Rohwer, could you make a quick comment?

DR. ROHWER: I just want to point out that in Dr. O'Lone's slides, her review of the WHO recommendations, there is no recommendation for three to six minutes at 132 degrees. The minimum time there

for any of the 132 degree autoclavings, especially with a force load autoclave, was one hour.

DR. FREAS: Thank you. Okay, that closes the open public hearing then.

CHAIRPERSON PRIOLA: I think we will take a break before discussing the questions, and reconvene in 15 minutes. That's 10:40, roughly.

(Whereupon, the foregoing matter went off the record at 10:29 a.m. and went back on the record at 10:45 a.m.)

CHAIRPERSON PRIOLA: Okay. So we are going to have questions presented to us now by Dr. Charles Durfor from CDRH, FDA.

DR. DURFOR: Good morning, Committee members. Before I begin, I would like to thank all of the presenters who have led up to this session. It will make this a very fruitful discussion for the Committee.

Just to give you a sense of what our thought process is leading to these questions, first Ms. Gill presented for you information about the broad spectrum of medical products that we are looking at, medical devices. As you consider the questions that are about to be presented to you, I hope you consider the breadth of these products, be they in their design

-- needles are not endoscopes -- be they in composition, ceramics, plastics, metals, different types of metals, be they in intended use.

So there is a great breadth here that we hope that you will be able to give us specific guidance in areas as well as some general comments.

Ms. O'Lone's presentation was focused on giving you information about general methods for validating the sterility of products, and we saw two different techniques. We saw methods by which bacterial contamination is eliminated and how that is done, and then we also saw comments in terms of virus validation studies for products.

While these two approaches are somewhat different -- in the case of bacterial validation studies, they are done on full scale material, and virus validation is often done scaled down -- they do have one important similarity, and that similarity is that, generally, data that looks at the sterility of a product, either for bacterial and microbiological infection or virus contamination, it is done on a product by product basis.

We do that, because often there is differences in composition or the way products are manufactured. So product by product information in

these two areas has been sort of the way things are done, which leads us to the topic today, which is a little different, but it's the question at hand.

That is the issue of applying -- When do we need product by product information for TSE products or medical devices for reprocessing?

We certainly recognize that the TSE inactivation studies will be most likely far more expensive, more lengthy in time, and the number of facilities equipped to do it may actually be reduced.

So that is certainly not lost on us, and that is certainly also not to belittle the cost, the time, and the effort required to do viral and bacterial validation studies, but we recognize that. With that in mind, we are coming to you today to ask questions that will essentially give us some of the following information.

So if I could have the first question, please. While you are reading this question, let me give you my thought process behind it. That is, essentially, there is significant published literature. Studies do take time to make more information.

So the first question is: Given the case where the type of product you are dealing with, the

type of medical device, either composition, indication or design, is sufficiently similar to what is already in the literature, and we have some level of confidence, what are the situations where we probably may not need additional new studies that we could apply particular published literature, published guidances to ensure that a product would be appropriate and safe for reuse?

Second question: Then we reach the flip side of that question. What are the situations -- and that is 2(a). What are the situations where a product may be different, either in design, composition or intended use, where it would raise concern that you may not be able to directly apply what is already in the published literature and the published guidances? When do we think it is appropriate to think about having a new inactivation study performed, that we need that information?

2(b) then asks you probably the most difficult of all question, which is how would we then go about designing such studies? In your discussions, it is my hope that you will provide some information for us, some guidance, about relevant models. We have heard a lot about different TSE strains, different animal readout and other readout systems.

Clearly, considering how the product is used in TSE inactivation study method of exposure -- we've seen numerous ways of doing that. How does the specifics of a medical device, be it composition, design or intended use -- how might that then impact the way you would design a study with regard to cleaning or even the method you use for inactivation?

Third question: The last two questions, in many respects, are related, and you may need to jump back and forth. In some respects, we recognize that. But the third question is a key question that, I think, a lot of people are wrestling with, and I'm sure you will as well, which is the question that was posed earlier.

How much inactivation -- How much reduction in infectivity is sufficient? That may well play to question 4(a) that you will see in a minute. That's why I was unwilling at this point earlier on to say that a one in a million or one in one million devices threshold is appropriate.

You may, as a committee, feel something else is more appropriate, and we welcome to hear your comments.

The other issue, item 3(b), is the issue, if you will, of surrogate endpoints. Right now animal

infectivity stands as the gold standard, but this is clearly a lengthy in time and costly process. So if there are other ways that we can use endpoint readouts for TSE inactivation studies, we would certainly welcome that comment.

If there are at this point none that you feel that are appropriate, it would be very helpful for us to have guidance from you as to what you think an appropriate threshold to consider would be for, if you will, establishing the validity of a surrogate endpoint.

The last question: As I said, the third question and the fourth question are somewhat related, and we recognize that. In this question we are asking would you consider what you know, what you've heard in the last day and a half and what you already know from your experience -- to consider what might be the anticipated level of infectious material present in different tissues and how that might then be related to its presence on a medical device.

Then 4(b) asks for guidance on how this level of infectious material should then impact your comments in terms of designing studies again.

So that, in a sense, is what we are after. We are trying to get a sense of how well does the

literature represent all products? What products does the literature not perhaps be totally appropriate for, and you need new studies? Then how -- If you do need new studies, how would you go about designing those studies? Thank you very much.

CHAIRPERSON PRIOLA: Thank you, Dr. Durfor. These questions are not for voting. They are for discussion. So the CDRH is really interested in the discussion, whichever direction it may take, that we have. I think we all realize that -- and as Dr. Durfor just reemphasized -- this is an extremely complicated, difficult issue to balance.

The published data with the requirements of the medical community, with the differences in devices, how do you design and provide advice for these sorts of questions.

So I think we just have to -- Everybody just has to give their opinion and debate back and forth, and see what we can come up with. I think there are some common things that can be considered.

So if we could open --The first question is already up there, and that is: What information in the published literature should be viewed as supportive data for establishing the methods and procedures for reprocessing medical devices that might

be TSE contaminated? Dr. Petteway, would you like to start?

DR. PETTEWAY: I'd just like to make a comment. I think that one of the speakers mentioned that the data that's published now was not reproducible. Maybe that might need some clarification. That data probably is, in most cases or all cases, reproducible data.

I think that the point was it's likely not transferable. So that in the context in which the data was generated, that's the context that you have to interpret it. In other contexts that you would apply whatever sterilization, you have to now interpret that in that context. I think that may be the issue.

CHAIRPERSON PRIOLA: I think that is an excellent point. That is partly what I meant by common ground. Where there are certain things that through all those studies the presence of what sterilization or sodium hydroxide are consistent. Dr. Edmiston?

DR. EDMISTON: I think the last speaker, Dr. Marchand from the University of Montreal, really set the tone for this discussion. I think most of us here are fairly keen on knowledge in terms of the

removal, disinfection, sterilization of biological entities, living entities from the surfaces of a variety of devices, but we are talking in many ways a physical entity.

We are not talking about a traditional infectious entity. I think, with that in mind, that is going to really couch a lot of our discussion.

You know, I don't even know where to start on this, to be perfectly honest with you. I mean, I have several pages of notes that I've taken throughout this entire discussion this morning, but I think there are some real key issues here.

It is obvious to me that there is a myriad of data that has shown, using a variety of markers, that you are capable of inactivating these agents. The issue is very little of that is applicable to the types of devices that we are talking about in the clinical environment.

We started moving in that direction yesterday afternoon, and with the presentations of Dr. Weissmann, to moving in that direction. I think my suggestion would be that we need additional data and studies within that arena utilizing those methodologies.

I really think all four questions are

interrelated, and I think it's really very difficult to separate out all four questions, because of this tremendous degree of commingling of our consensus here.

So I would propose that, while there is significant data out there showing levels of inactivation, I would suggest that we don't have enough data or the right kind of data looking at inactivation of these particles on the types of materials that we are specifically interested in, those materials, as Martha and Ms. Gill pointed out, the types of materials that we see, especially in a neurosurgical arena.

If I move very quickly and let someone else speak, on one of the slides that Martha presented, sterilization validation, she indicated what is the acceptable sterilization process for prion removal inactivation? I like the term acceptable.

It's the other issues that fall under that which none of these previously published studies really address. I think that's the dilemma that we are facing. We don't have sufficient data on those devices or the types of materials in which those devices are composed of to really say, based on question 1, we can submit a consensus.

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: The morning's presentations were very informative and very stimulating, including the last three from the public. They lead me to one comment and one question.

The background for the question is my sense from the discussion that people think about these TSEs as getting sort of plastered down on hard surfaces where they get stuck, and they are hard to remove.

I wonder if anybody has looked at the possibility that they are, in fact, getting into micro defects on the surface where they can lurk hidden until they come forth. And if that is, in fact, the case, it might explain why higher temperatures which would expand a metal and tend to seal those up are not as effective as slightly lower temperatures. Maybe somebody could comment on that later.

The question -- The comment really is in the form of a request to FDA. If I understand that 10-6 standard, it is in terms of the presence of an infective agent. It is not in terms of transmission or in terms of risk to patients.

I wonder if whether, for TSEs, that standard should be reviewed and possibly recast. I'm

not arguing about the 10-6 number, but rather about whether it is referring to the right thing. So FDA might want to give that some thought.

CHAIRPERSON PRIOLA: Dr. Gambetti?

DR. GAMBETTI: I agree that there are now probably not sufficient data that are really directly pertinent to surgical -- neurosurgical instruments -- experimental data, I mean -- to really come to a conclusion that would really apply directly to that instrument. But the question is do we have -- Ideally, we should have these experiments done, but can we wait for them?

Do we have -- That's what I would like to know, whether we have to come up with some direction with what we have now or do we have the luxury to wait for the result of really experiments -- experiments that really try to reproduce the conditions of surgical instruments in an operating room.

DR. WOLFE: The reason I asked Dr. Weissmann after his wonderful presentation what he would recommend for use in a hospital is that the answer to that question is the at least attempt, not in this forum but at a local institution, to make the leap from the experimental evidence to what is on the ground.

I assume that at the VA Hospital in Baltimore that there are some procedures that Bob Rohwer could tell us have been put into place as a result of what he knows. I would like -- It's not a complicated request. It's to try and collect from what is going on in the country right now, in Cleveland, in Baltimore, in other countries, what operationally is being done. That's the first request.

It seems to me there are three sets of variables. One set of variables is the devices themselves. I mean, the really elegant, straightforward, common sense presentation by David Asher and Stan Brown yesterday started telling us that some of the things that people think theoretically would be good to sterilize wreak havoc with certain kinds of instruments.

David Asher just told me that that electrode that Dr. Weissmann took off his experiments from that infected two subsequent patients had all kinds of nooks and crannies. That's exactly what John Bailar just said. You would expect that, if there are nooks and crannies, that when you re-sterilize it, there are even greater possibilities for hiding things.

So variable A is: What is the nature of the device that might make it more likely to harbor infectious agents and/or be destroyed or messed up with a cleaning procedure?

Two, which is one of the slides that Lillian Gill had this morning, is sterilization devices themselves. Are we going to invent or think about modifications of or brand new sterilization devices that could be certified or at least shown, based on scientific evidence, to be able to get rid of prion-like materials?

Third is procedures. I mean, it seems that the output of this discussion in the four questions and subparts is what do you do in a hospital, taking into consideration the kinds of devices you are using in surgery, neurosurgery and surgery, the sterilization equipment that you are using, and the procedures, using existing known things, whether sodium hydroxide or bleach or whatever else.

At the end of this discussion, whether it's today or the next time, hospitals would like to know what we think -- a modification of WHO or whatever -- should be done. It is going to involve those three elements.

From FDA's regulatory perspective, they obviously could put out regulations that would say, if you are going to use neurosurgical or, because of the variant-CJD, going into other tissues, a general surgical device, you should be able to get rid of little nooks and crannies or have to throw it away.

It could put out a regulation that says, if you are going to claim your sterilization equipment is capable of getting rid of prions, it should meet certain standards. But it also can put out guidances parallel to the WHO guidance that says the combination of all these should be done in the following way.

I'm just raising these issues to try and focus a little more on these different elements that we are considering.

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: We have had, certainly, some elegant presentations today, and some discussion of risk. For me, it really factors in on the risk.

Yes, it's possible to treat surfaces to inactivate the prion, but on the other hand, what is unknown is the detrimental effect of those procedures on such devices and the risk of having them within the medical environment.

So in essence, we are dealing with what at

this point seems to be a relatively small risk. With taking this other step, we may introduce new hazards that are at this point unknown.

So I would at this point urge caution. And again, as we have heard, I think, expressed here, we need to have more data on the impact of these interventions on all the various devices that we are speaking of, because again as my colleague here mentioned earlier today, there just doesn't seem to be a high incidence of problems related to this topic, this risk today. The risk seems relatively low.

So, again, I am quite concerned about introducing a whole new set of hazards or risks without more data.

CHAIRPERSON PRIOLA: Well, I think that is exactly what the CDRH is asking us to do, in one way, is to give them a starting point to start assessing this in regards to all the different medical devices that they have to regulate and be concerned about.

The starting point, it seems, for them is to ask simply, with what is available now that's published, can there be some general recommendations for how they can begin to design and establish studies to look at these issues of inactivation, and whether what is published in the literature is directly

applicable, it's probably not. As Dr. Gambetti said, there are so many different variables, but there are common themes.

Inactivation with bases tend to be better, far better, than with acids. Wet sterilization -- Obviously, that came through very strong -- is better.

So for starting points for studies, those are the sort of things that could be considered: Oxidizing agents, protease -- protein degraders, things like that, enzymes. That's where they have to start to begin, I think, to think about exactly what everyone here has said, if I've understood the comments so far.

In part -- I mean I don't know what everyone else thinks, but I think that the available literature does give them a direction in terms of start looking at base -- inactivation with bases that aren't quite so caustic and dangerous as NaOH and might be able to be more easily handled in a hospital environment, because that is another consideration, looking at new enzymatic treatments in a hospital environment, things like that. Yes, Dr. Wolfe?

DR. WOLFE: I fully agree, but I also -- just going back to the first point I was trying to make. I think that the translation from the published

literature into practices and procedures in hospitals would be very telling. Those practices and procedures are probably themselves not necessarily published.

So I would not necessarily expect that in the U.K. the answer to the question I asked Dr. Weissmann, that has actually been published anywhere. I wouldn't necessarily expect that in Baltimore you have actually -- the hospital has published how they are translating your research into on the ground.

So I think that it would not be that difficult to at least collect that to use as an adjunct to the published literature which -- I agree with you -- gives lots of clues, lots of information. I also agree with Dr. Bracey's suggestion that we don't want to do something that would be a step backward by creating a greater -- you know, having the treatment be worse than the disease, so to speak. But I think that those kinds of things have probably already been taken into consideration, hopefully, in those places that have changed their own procedures, which is probably most hospitals in the country, some different than others.

It would be interesting to see, for instance, if there are significant areas of difference between hospitals in terms of what they are doing

right now and, if so, are these science based or are these sort of whim or hopes or whatever. I think it would be very illuminating.

CHAIRPERSON PRIOLA: Dr. Stroncek?

DR. STRONCEK: Based on what this Committee decides and the policies implemented for, you know, possible TSE infection of blood donors, it's been very cautious. They have really been extreme to avoid any transmission through blood donations. You know, we have excluded donors and created lots of extra costs.

Well, I think in this situation there is some good data that there are ways to inactivate the prions, and that people are using them on a regular basis in a research setting. Yes, there is always a need to get more data and do more studies, but I think we are at a point where some recommendations can be made.

You know, it's been said that what the hospitals are doing now is working, because we are not getting any transmissions, and I'm really not convinced about that, because it's often that, because of the long incubation period and because people that go in the hospitals are often sick and don't live very long after that, that there may well be many cases

that's being transmitted that we don't know about.

So I guess I would feel like -- feel more comfortable if the FDA starts to move forward on this question.

CHAIRPERSON PRIOLA: Dr. Khabbaz.

DR. KHABBAZ: Yes. My sense from this -- I find myself supportive of the comment of the recommendation of Dr. Edmiston and yesterday Dr. Gambetti of the need for additional studies.

I was quite impressed by the elegant presentations and how much of the approaches taken and the methods that are out there, and I agree that they can be used. But my sense is that what we have in terms of going with caution, as was just said, are the WHO recommendations and the CDC draft recommendations that are in line with the WHO recommendations.

What I heard today, some concerns. Are they too stringent, and are there some downsides to them? I think, you know, the only way to get away from that stringency is to have some studies designed that are directly pertinent to the procedures and to the instruments.

So we have an idea of the approaches, but to be able to step back, I think we will need studies. I was also heartened by the industry offer for

partnership, and I think, as the FDA moves forward to support or design studies, I think that kind of partnership and bringing together -- not just looking at published literature but bringing together experts from academia and industry is going to be important, I think, to try to standardize approaches and studies.

DR. EDMISTON: I think the problem the FDA has in this arena is, as was correctly pointed out, there have been a number of studies showing that you can inactivate these agents, but then there's the validation component. There's the validation analysis.

If you think about a hospital, how a hospital works and how it manages its central processing, we use biological indicators to suggest to us that everything is working fine. But we don't have those types of devices available or biological or even physical indicators that may be available for prions.

So the issue is how do we translate that to the practical perspective? Is it appropriate to try and discuss this in the context of all four of these statements or are we really limited to going through one question at a time?

CHAIRPERSON PRIOLA: Oh, I think the conversation is already roaming all over all four

questions. So I don't feel any need to go one and the two.

DR. EDMISTON: What we really -- If we are going to establish validation studies that industry and both the private sector hospitals can live with, then we are going to need some consensus and not the consensus from this panel. We are going to need the consensus from experts who are knowledgeable about this issue.

I think the models -- What I'm really concerned within terms of validation is do we need an animal model or can we live with a cell culture model? If we can live with a cell culture model, that can corroborate with an in vivo model such as a mouse model. If that is acceptable, then we need to place that into the discussion. But we can't decide that in this Committee.

I think the data is very clear that there is some evidence that there are some corroborations between in vivo and in vitro models, and I think we need to address that.

We also need to address the threshold value, the endpoint value. If you look at Dr. Weissmann's data, as I inquired about that, I would suggest that one would be looking at thresholds of

zero, but then that is not an acceptable risk.

We are almost dealing with almost a chemical entity in that, the same way the EPA or some of the other agencies discuss exposure to certain environmental contaminates. We may be moving in that direction with TSE. So we need a consensus there.

We also need consensus on other issues in terms of what are the optimal -- I'm not going to use the word sterilization; I'm going to use the word decontamination -- the optimal decontamination strategies.

I can live with the CDC guidelines as they are written, and I have a little more confidence than you do in terms of our abilities to continue to see few cases in the near future, based on some of our infection control processes. But I'm afraid this Committee as a group is really not competent nor knowledgeable to provide that kind of information at this time.

Where we are competent is to recognize our deficiencies, and I think we need to look at those individuals who have done these studies in the past, look at endpoints, look at threshold, look at validation assays, so that that information can be provided to the FDA; because they are in a position

where they have to make a call, and I think they are very uncomfortable with making that call based on what is currently available. Am I off target on this?

CHAIRPERSON PRIOLA: If I understand correctly -- and maybe CDRH and FDA can help me here -- these questions don't have to do with regulation by the FDA. These are posed by the CDRH asking us for ways to help them to design studies to decontaminate medical equipment.

So I think with FDA -- In regard to FDA making regulations or recommendations, that doesn't apply to this topic, maybe to Topic 4. To CDRH, maybe you can again clarify. This is Dr. Durfor.

DR. DURFOR: Yeah. I'm not sure it's easy to separate the issue of regulation and design of studies. I think what is important is providing information such that -- and taking advantage of the wealth of knowledge on this Committee to understand -- I mean, you could view it as regulation in the following manner. That would be that someone wishes tomorrow to come in with an application to say we wish to claim that we can sterilize scalpels from TSEs. That's a real world situation.

I'm not sure whether you view that as regulation or designing studies, but it would be

exactly what we would hope you folks could help us with in terms of when is a published literature supportive. When is the published literature -- What is it about a product that might make you say, gee, you know, I really feel uncomfortable with what's out there; maybe we should have them wait a period of time until there are more data.

CHAIRPERSON PRIOLA: Dr. Gambetti.

DR. GAMBETTI: It looks to me that these series of questions and the information, the amount of information that we have received, is very complex, actually too complex to approach.

I would recommend that we simplify the issue. One example of a question that I think we could deal with is whether all the information that we have heard yesterday and today is sufficient to come up with a procedure of decontamination that we think is safe.

For example, as we have heard, washing the instrument, treating with sodium hydroxide, autoclave, and then regular sterilization -- Do we think that the evidence that we have heard so far, although did not apply directly to a scalpel used in a neurosurgical procedure, but certainly stainless steel wires is fairly close. Are those -- the information available

now sufficient to tell us that -- to reach a consensus that there is a procedure that gives very reasonable assurance that the instruments are decontaminated or we don't have enough -- we don't even have that.

That is my question. Do we have already enough information to say that, if we apply a certain procedure, we have very good reasonable evidence that this will decontaminate the instrument that may be infected, or we don't have any information really at this point that is applicable to the surgical instruments?

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: Again, two points. I'd like first to come back to the comment I made earlier about micro defects. I am talking about what looks like hard, polished, smooth, perfectly clean surfaces, but still have countless cracks and pits that might be just big enough for a protein to hide in.

The answer might make a difference, because how you go after something on the surface might be different from how you would go after something that is lurking just below the surface. I don't know that's the case, but I find it an interesting question that might be worth some thought on the part of FDA or some thought on the thought of

experimenters who could look at this.

The second thing is that I do accept the notion of some level of residual risk. FDA quite properly considers the whole complex mix of costs, risks and benefits. These have to kept in balance. There are costs and risks associated with higher expenses for processing things or for new equipment, from withholding things that the public might on the whole benefit from.

On the other hand, I don't think these should generally be in perfect balance. We have a long history in which regulation has forced technology in directions that have been previously considered unattainable. It's just the way the world works. Thank you.

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: In terms of process, I think there are really sort of two schools of thought in terms of how to handle these materials and trying to look for perhaps a simple aspect. The issue of reducing the burden of tissue prior to initiating the sterilization or decontamination is something that perhaps the Committee could consider.

That is, would we endorse reducing the bulk prior to initiating the decontamination act,

because in essence there are disparate approaches, and I sense that is one thing that we could perhaps handle.

CHAIRPERSON PRIOLA: Dr. Wolfe?

DR. WOLFE: Some of you will be tired of my saying this, but it's in the context of acceptable risk. On one hand, we have never, fortunately, had a case of blood transmission, and there are some theories as to how buffy coat injected intercerebrally can cause disease, but there are no cases, and a number of very cautious, I think, mainly appropriate steps have been taken to sort of cut off that kind of possibility.

On the other hand, despite the fact that the U.K. banned cadaveric dura mater 15 years ago, and Japan about a decade ago or almost a decade ago, this country, this agency still says it's okay to stake a piece of dura mater from someone who well may have been incubating CJD on someone else's head, and we have not zero on the case of blood but 110 or 114, depending on how you are counting, known cases of CJD that have been transmitted.

Now I'm not mentioning it just because I am again making a plea to get this stuff off the market, but more to put in context, and sort of

responding to Dr. Bracey's statement -- putting in context the acceptable risk.

There already are some decisions made on prion infected or potentially prion infected material in terms of its acceptable risk, and I think the two ends of the spectrum really are dura mater and blood: One, no transmission, a lot of precautions which -- and the reason I raised yesterday, are we collecting data on what would it mean if we deferred Canadian donors or people, is that that could tip in the direction of more harm than good, depending on the benefit and risk balance. On the dura mater, it just seems like a no brainer, so to speak. Bad pun, but it should be taken care of.

Here we are somewhere in between. We have some cases. There are more from the old days. Dr. Asher assured me that we can't go back far enough for some of those early cases to find out what kind of sterilization techniques were used on them that still resulted in transmission, but I just want to put it in that kind of perspective so that, whatever we decide and whatever evidence based validation procedures and so forth, that we actually do something that makes sense.

CHAIRPERSON PRIOLA: Dr. Edmiston.

DR. EDMISTON: I'll make one more comment. You know, everything that we have been doing in medicine over the past ten years is evidence based, and there is probably nothing wrong with having evidence based decontamination processes.

I would like to suggest that the way we approach this is that we pull together a panel of experts, and not us, but a panel of experts who are knowledgeable about both in vitro and in vivo assays, who are knowledgeable about material science surfaces -- I really enjoyed hearing Dr. Brown's presentation yesterday. It was one of those things I was looking for. They are moving in the right direction -- and also a group of experts who have the knowledge of endpoint determination and risk.

I think the risk issue is very important. I am comfortable with the policies and procedures that we've had in place in many of our institutions, but I think for the FDA's perspective to be able to license, to look at new technologies as they come down the road, there has to be some mechanism to put in place validation studies, of which there really is no mechanism at this time.

So this is going -- I hate being on committees where you can't a decision. I absolutely

hate it, but I think in this case you are making a decision. That decision would be to convene a panel. It has to be international, because I've loved sitting here and listening to my colleagues from Europe present some of their findings, to be perfectly honest with you, many of which I wasn't even aware of. But I was really impressed that they bring an awful lot to this process.

So I think it should be a highly collegial process. It should involve our colleagues both in Europe and the United States, and those individuals who have a focus and maybe even a proprietary interest in this particular area.

CHAIRPERSON PRIOLA: Kiki, did you want to say something?

DR. HELLMAN: Yes. First of all, I am heartened by this discussion. It is always difficult to take data from the research setting and apply it to the real world, and I think that this particular meeting has been very helpful, because I think we have really brought it to focus in an area sometimes where we might face it as individuals, as patients in a hospital needing a particular procedure.

So in that sense, we can personalize it. I think that these comments have been very helpful.

I think there are some -- and getting back to it, to put it into perspective, there are some data out there that are good data, that tell us a lot about decontamination of these agents, and I don't remember who of the panelists made the comment, but maybe it's the context in which these studies were done.

Let's look at all of these different studies and see if they are comparable from the same context, from lab to lab. Look at procedures and see if there is internal consistency, and then look at these procedures, bearing in mind the different instruments and procedures that are done in a hospital setting and see whether there are some design characteristics in instruments that need to be looked at with regard to sequestering infectious material. Here, it could be TSEs. In the future it could be something else.

So that industry then would have a very important role to play in the developing of instruments and other devices that would also reduce the transmission potential.

So that I think, certainly, there is information from basic research. We need to take a look then at the instruments per se. We need to take a look at how those research data can be applied and

translated, as Dr. Wolfe said, to the hospital setting.

Do we need to do something else in the hospital setting? We need to take into consideration the individuals that are going to be working in the hospital, and we need to also take into consideration the industry who is going to be reprocessing. Some of the reprocessing is done in the industry; some is done in the hospital.

So we are talking about a problem not only in the research setting, not only in the hospital setting, not only in the industry setting, in a number of different settings; and it might be very helpful to have more of a dialogue to see what is applicable in these different settings, and see if we can't come to agreement with some definitive guidance, if you will, or guidelines, if you will, that will actually assure all of us that the next time we go into the hospital to have our appendix removed or something else done to us, we can feel fairly comfortable that we will walk out and walk out better for it.

CHAIRPERSON PRIOLA: Dr. Marchand, do you have a comment?

DR. MARCHAND: It's a comment about the washing techniques. The most -- The biggest variable

in the hospital set-up is the washing techniques. Now let's just hypothetically accept a risk level of one in a million, and we may find out that if we wash properly and sterilize with our normal process, we can go below this hypothetical risk and not having to change any process.

So I would suggest to the committee here to have data on what is residual organic material on instruments as it has been published recently in some GIC journals, and some groups are doing at Northwestern Case University, and see how they are effective, these washing techniques, and maybe we just -- this committee could end up with just recommendation reinforcing washing at the end, if a risk level is accepted. This can be a reality.

CHAIRPERSON PRIOLA: Dr. Rutala?

DR. RUTALA: Yes. I just wanted to make two clarifying comments. One comment responds to a question from Dr. Bailar regarding surface topography and essentially the pitting associated with stainless steel.

Certainly, we and other investigators have looked at stainless steel, and you are absolutely correct. There is a great deal of crevice and cracks and pitting associated with stainless steel. Not only

can proteins reside in those crevices, but microorganisms can also, and you can actually see a difference in results.

It's one of those factors that affect the efficacy of disinfection and sterilization, depending upon the quality of the stainless steel, depending upon how much protection that those crevices and cracks provide. So you can actually get differing results based upon stainless steel composition.

To Dr. Wolfe's comment, we certainly agree completely with, of course, the importance of practices in hospitals in the United States, and make those practices evidence based practices. The draft CDC guideline that was mentioned a couple of times has almost 1,000 references.

So just the issue regarding disinfection and sterilization of prion, there are 60 references. All the papers that were cited at this meeting were referenced in that guideline.

So we are incorporating into U.S. hospitals, and have been for really years, the information, and that is incorporated by, of course, evidence based guidelines that are promulgated not only by organizations such as the Centers for Disease Control but other infection prevention organizations,

to include the Association for Practitioners of Infection Control and Epidemiology, SHEA, the AORN Organization and so forth.

So we agree completely for the need for additional research, additional research that would reflect clinical practice. But until those additional studies are available, we have incorporated the basic inactivation studies into the existing guidelines.

CHAIRPERSON PRIOLA: Dr. Durfor.

DR. DURFOR: Thank you. One of the concerns about sort of addressing all of the questions at once is that some issues may be left unresolved and undiscussed. If it would be possible and if it would be acceptable to this Committee, I would like to then direct your attention to question 2(b), if we could have that slide.

Essentially, I think that follows just what we heard, which is to draw upon this Committee's experience in terms of what aspects you might offer us in terms of how studies could be designed.

CHAIRPERSON PRIOLA: Thank you. Actually, I was just going to get to that. Thank you, No, that's okay.

Getting back to what Dr. Bailar had mentioned earlier about the differences in medical

equipment and micro pitting and what not, I think the first part of question 2 -- 2(a) -- discussed what aspects of the medical device and its use should be considered.

I think that perhaps, in my mind, the important thing is the use, and that is that was defined by, I think, Ms. Gill in her presentation where they said their primary consideration concerns have to do with neurological medical devices.

So that any device that is used in a potentially high risk patient that is having a neurological procedure, that device should be considered at risk. The aspect -- What aspect of that device is at risk is, I think, almost impossible to determine without direct experimentation on the materials that make up that device.

I think Dr. Weissmann stated -- suggests very strongly that different materials will adhere prions equivalently, plastic versus steel, for example.

So it may be that with that data in mind, that examining every specific material in a specific medical device might not be that helpful, but just assuming that any medical device that is used for a neurological procedure is at risk, and determining

what sterilization procedure would best be used for that device might be a primary issue.

I'm sorry. You are?

DR. CERENAKOVA: I am Larisa Cerenakova from the American Red Cross. I still would like to go to the first question, if it is possible, because I have some comments to that. Is it possible?

CHAIRPERSON PRIOLA: Well, if you are very brief, because we have moved on to the second question.

DR. CERENAKOVA: Yes, I will be brief. I would like to divide this question on three different parts, because how the question is posed, it is not really clear.

If we start form the end of the question about the procedures which will be used, you know, for operation we suspected CJD. In my opinion, if we know that this case is suspected of CJD, this device should be probably destroyed or not used for another patient.

The second part of the question raised the issue about -- Can you go back, because -- It will be brief, but it might give just a clue what I would like to say. The second part of the question was dealing with the procedure itself.

I think the question should be raised in

it if procedures which are used presently in the hospitals are sufficient to decontaminate the prions.

The third part of the question deals with the published data which will support this or that. I believe that we have sufficient amount of data from epidemiological studies, from infectivity studies in mice and now we heard a lot of the studies which were done in terms of the contamination procedures.

In this case, it's just things that it will be probably necessary for the FDA or whoever is working this to put all these three things together and make some recommendation or to raise the question properly so that it will be properly answered.

CHAIRPERSON PRIOLA: Thank you. Is there any discussion from the Committee about either (a) or (b) of question 2? Dr. Hogan?

DR. HOGAN: Well, yeah, getting back to this, in terms of neurosurgical instruments I think the questions are -- everybody is addressing this -- whether or not you are going to -- An instrument that's been used on a known CJD patient or probable CJD versus routine inactivation. It's a very different approach.

The problem with neurosurgical instruments is, more and more, they are going toward titanium

instead of stainless steel on some of the finer instruments. They stand up to rigors much better.

So I think I would encourage the researchers to look not only at gold and stainless steel but also titanium. It may be the same, but that is going to be important in terms of validation in the future.

Secondly, all of these instruments, with a few exceptions, the ones you use on the skin, are extremely complex with lots of nooks and crannies, lots of hinge points, lots of serrations. So there's a lot of issues about what can hide. The same is true in ocular tissues -- ocular instruments.

So this is a very complex question, and that just gets at the instruments that are metal. What about the neurosurgical endoscopes that cost $20,000 each? How are you going to routinely inactivate those -- deactivate, decontaminate? Those typically are -- There's some water and some chemical inactivation/deactivation now in those as well, but if you subject them to the kinds of things that we've been talking about here today, they will be destroyed.

So this is a very difficult question, and I would urge again -- To second Dr. Edmiston's encouragement as well as industry's, I think we need

a forum with experts that are from the industry, individuals that use these instruments, hospital personnel that have to decontaminate them, and researchers that do the validation studies to come up with some guidelines, because I don't think that I certainly have any competence in making any suggestions for this. I'm just hopeful that that will occur in whatever way.

DR. EDMISTON: I think, in terms of your response about question 2, I think the agency in the presentation by Ms. Gill has clearly defined the instruments that we should be concerned with, neurosurgical instruments, especially those that fall within the critical risk category.

CHAIRPERSON PRIOLA: Getting back to what you said, that you don't feel comfortable giving out recommendations based upon what we heard, certainly, in the TSE field we heard from really just about all of the experts on inactivation that we have in the TSE field that have worked on this problem for quite a long time and quite deliberately, Dr. Rohwer or Dr. Taylor, Dr. Somerville, Dr. Weissmann.

What you heard basically summarizes, as far as I know, what we know in the TSE field for inactivation and its uses against different strains of

agent. So that can be used, I think, again, for a basis of beginning to give at least a framework for people to think about designing validation studies, which I think in part is what's being asked here.

In terms of a question that came earlier, which was the endpoint versus -- endpoint in vivo assay versus in vitro titration, that is also something that we struggle with constantly in the TSE field.

Actually, Dr. Weissmann's assay is the closest we have ever gotten to what people have in bacteriological and viruses, which is the titer assay, an in vitro titer assay.

So studies that try to design ways to titer the prion infectious agent should be strongly encouraged, but it should be acknowledged that they are extraordinarily difficult or we would have one by now that would work with every strain.

So you're right, it's an incredibly complicated problem on every level, starting scientifically and just all the way up the ladder.

DR. EDMISTON: I think the consensus component is extremely important, and I'll tell you why: Because you may actually come to a threshold level, an endpoint level, but in the real world that

stage still may result in infection. So that's the problem that occurs here, and that's why it is extremely important to have the consensus of the true professionals who work day in and day out in this activity, because there is going to be this level of accepted risk.

I'm going to tell you something. We all need to be sitting at the same table, and we need to agree, even during those periods of disagreement, but in the final analysis we need to agree on how we should validate these procedures. I suspect it's not going to be an easy process, but at least we are fortunate that we are dealing with a rather small group of professionals as opposed to the group that was involved in developing the Vancomycin Use Guidelines in 1994.

So I think we are fortunate that most of these individuals are sitting right here in the room.

CHAIRPERSON PRIOLA: Dr. Hogan, did you have a comment?

DR. HOGAN: No. I fully agree with you. My problem is, though, none of these individuals are standing up and talking about this. They have presented their data, but they have not given -- outside of the question that Dr. Wolfe asked of Dr.

Weissmann -- their opinions on these guidelines. That's my point.

In ending, I just would encourage -- We've seen a lot of stuff about strain differences, 263k. I think that I would encourage you to continue to try and find neuroblastoma cell lines that you can put 301v into, so that we can really get the most robust strain, the worst case scenario model as a useful tool for validation.

CHAIRPERSON PRIOLA: Boy, I wish it were that easy. No, I think it should be strongly encouraged, and rest assured that a lot of people are working to do just that in many, many laboratories. It's a problem that -- I mean, I'm working on it now, and we've come up with -- We have different ideas and different ways, and it's unbelievably difficult to get to work, for reasons that we don't understand, because the basic nature of the agent is still vague.

That gets to Dr. Bailar's question about whether this agent can hide out in nooks and crannies. Who knows, because we don't know what the infectious size is, really, in any way.

In terms of the validation issue, which gets to this question 3, the magnitude of log reduction versus surrogate markers, does anyone have

any comments on that, on a potential surrogate marker? One of the gentlemen who discussed it -- I think it was maybe Dr. Marchand in the public hearing -- brought up fungal prion proteins, for example.

Is there anything that we can think of other than infectivity or PrPres that might be sufficient? I can't, offhand. I mean, I think that's a question that there's just not enough scientific data to even begin to address.

What about validation studies, limits infectivity? Yes?

DR. LIN: If I can give you some background, I think that Dr. Chuck Durfor -- in his presentation he very much give you some background as to why we asked that question. Maybe I will use it the other way or maybe explain why we asked that type of a question.

I heard so many people talk about it, including Dr. Wolfe pointed out real life situation. I think that's exactly what we question right now. Actually, you already point out -- Several speakers already point out from yesterday and this morning two recommendations.

One is -- One is organization, recommendation for prion decontamination. The other

one is that Dr. Rutala pointed out a serious recommendation on -- which is different.

Now in terms of real life situations, we have a manufacturer come in to us, say, well, make a recommendation or here is a recommendation -- make a recommendation, say that this method is as good to decontaminate those contaminants, TSE contaminate device or potential decontaminate device.

So they want to come to us, say, well, can we use those methods to decontaminate those device, the neurosurgical device? Now the question that we say, well, then you need the validations. Now they say, well, now how do I validate? You don't have guidelines. Right?

How do we validate? What kind of endpoint are you accept? And that is our real life situation, and that is the reason we ask your input to hear whether you can give us some guidelines based on what current -- We heard so many presentations. For example, we talk about a spike -- spike was unknown or bacterial spore. Then the endpoint and the whole cycle. But in this TSE situation, what kind of a spike agent you can use?

I heard people mention about that you can use infected wire as a surrogate or you can use a

fungal, as Dr. Marchand pointed out, a fungal protein as a potential surrogate indicator agent for those validation studies, and that is where maybe, if the Committee or the panel can give us some guidelines in that area.

CHAIRPERSON PRIOLA: I'm sitting here thinking about -- When you say, you know, validation -- some of these validation studies include following what happens to a spore that's taken through the process. Of course, the big, big difference between that and the TSEs is the lack of a rapid assay to find out if you have anything left.

So, certainly, it's been discussed here many, many times that you can spike these solutions and then look for infectivity later, but that will take minimally one year. That's minimally.

So the lack of an in vitro assay makes it very difficult to determine what sort of marker you could use for a validation study that is based on infectivity or even PrPsc. I have my doubts. I know that it says here would the presence of PrPres be acceptable, and there is a very good correlation with PrPres. When it is present, there is infectivity, but you don't have to be able to see it to have infectivity. So my opinion on that is, no, I would

not use PrPres as a surrogate marker.

So then in my mind the question becomes can you think of another way to seed with a surrogate marker that you can take through the same procedure to see if you can get something that is not PrPres but acts like it and use that as an endpoint, which was why I just sort of asked if anybody had any wildly strange ideas about it.

But the difficulty, of course, is the assay. That is something that most definitely can't be resolved here. Would anybody else like to comment in the Committee? Any ideas?

DR. PETTEWAY: Dr. Priola, down here on the end. Yes, your comment about PrPres and not using that as a marker -- PrPres is, in fact, a surrogate marker. There is no absolute indication that it is the agent. It is a surrogate marker, and we correlate with that marker.

The issue that you are addressing is that there could be infectivity that could be important for transmission that is not associated with PrPres. Is that --

CHAIRPERSON PRIOLA: That's possible, or that -- That's true. I think that's true. You will get disagreement from people in the field as to that.

I think it has absolutely been shown that you can go through and try to detect PrPres and not see it at all, and you get infectivity. The issue is, is it because it's not the infectious agent or you're just not sensitive enough in detecting it.

DR. PETTEWAY: That's right. And that kind of brings me to what I've been hearing. You hear a lot about validations, and we need to validate. I think that, as someone who kind of struggles with this whole issue of what validations are and are not, at least from the context of our processes in the plasma industry we really can't validate that any infectious agent is removed by a process.

What we can do is we can provide scientifically valid data that provides assurance that that agent would be inactivated or removed during processing. I think that's probably what is going to happen here, especially with using materials that are representative in medical devices, that the bottom lien is that you will be able to provide scientifically valid data that supports a minimization of risk, which kind of brings me to the next point.

It's actually in the subsequent question, which is -- Oh, we are 3 now. Good. It says: "If so, what magnitude of log reduction would be

considered safe?"

Well, safe is kind of absolute, and I don't think that we can assure absolute safety by doing what we are calling validation studies. What we can do is provide some assurance for the minimization of risk of transmission based on whatever the process is. I think that's what we need to keep in mind.

It could be that 2 logs of reproducible robust reduction would, in the end, provide a safe product. Four logs may. So I think we don't want to get mixed up in trying to recommend numbers without understanding again the context and what the starting risk really is.

CHAIRPERSON PRIOLA: Dr. Edmiston?

DR. EDMISTON: You know, I think that in some way is how some of the other governmental organizations function. The EPA -- they look at the relative risk, threshold levels. In the air pollution industry, they look at relative risk, threshold levels.

This is a bit different from what we have been working with in the past. You know, we are looking at trying -- We use a spore, a bacillus spore or other spores, as a marker of the effectiveness of our sterilization process.

We don't have that kind of marker present, which is a concern for me, because those of us who would be using a device that industry may present, and they may have a validated procedure -- what do we have in-house to validate their validation or do we have to validate their validation? Are we excluded from that by virtue of the complexity of this particular entity? These discussions will come up.

So I think you are absolutely correct in that we are going to have to deal within the realm of relative risk. This is why we really need to have a very finite discussion on some of these issues relating to infectivity and relative risk.

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: Since 3(a) is up there, I would like to comment that I think it's simply miscast. What matters is not how much is taken away but how much is left. Reduction from, you know, 10-1 to 10-3 may not be any help, because there is enough left for everybody to get sick anyway. 10-10 down to 10-12 won't help either, because the risk is so small to begin with that there can't be much benefit from it.

I'd like to see that changed to -- the thinking behind it changed not to the log reduction,

but to what is left.

CHAIRPERSON PRIOLA: Dr. Weissmann, would you make a comment?

DR. WEISSMANN: I think one should proceed in two stages. I think one should reach a consensus on the best possible recommendation we can make at this time, and call it a tentative recommendation, or provisional.

The real test, I think, has to be very pragmatic. I have proposed in the U.K. without any success, I should say, that the way to go about it is to use -- Well, we were thinking of metal beads, the aggregate surface of which correspond to a surgical instrument, say 10 square centimeters. Expose that to infected brain or brain infected, for example, with variant-CJD, put it through the recommended procedure, and plant it into primates, and see whether, let us say, among 20 primates all of them remain healthy.

I mean, this is the pragmatic way, because we can't necessarily speak of reducing 6 logs or 8 logs, because we don't really know what we start with. But here is the really pragmatic thing. You loaded the metal with the maximum infectivity you could expect to get on it. You go through a procedure, and you show that all the animals survive it.

That is, by far, the worst case scenario, because nobody is going to expose a surgical instrument to an infected brain homogenate, and nobody is going to leave the instrument for 12 months in the brain of a patient.

So it seems that kind of test would be the worst possible scenario. If the procedure is effective, then I think it's a pragmatic way of saying the procedure is valid.

CHAIRPERSON PRIOLA: And something like that would also have the advantage, you could pick the materials you want. That would represent whatever medical device was going to be used. So the endoscope issue, for example. Yes, that's very true.

Other comments from the Committee? One thing I was thinking about after what Steve was saying about validation studies is that all the experiments we heard yesterday with the gelatin industry and those sorts of studies where they are using transmission of infectivity to animals as sort of -- as the criteria for whether they have cleared the agent from the spiked tissues.

That seems to me to be the approach that can be taken here for these medical devices, using the sort of model system that Dr. Weissmann has used with

his metal rods and the suggestion he just made. Would that be something that industry could deal with?

DR. PETTEWAY: Yes. In other words, those were scientifically valid studies. We call them validation studies that mimicked the manufacturing process. Identified parts of the process or methods that could inactivate or remove prions, and by doing that, assured based on what the load, the theoretical load, would be or, in this case, the real load, that there was a margin of safety. That's what you are trying to achieve, is margin of safety.

Just let me comment. You guys have seen that with removal -- you know, with studies that we have done with removal, we were able to correlate the removal of PrPres and infectivity in the same sort of experiments. Clearly, from the inactivation perspective, I think studies that Dr. Kempf presented with inactivation by sodium hydroxide, that would also be very -- I think, very effective, if we were able to do that. We don't have that now.

So you're right. So there is not a corollary with these procedures, inactivation or degradation of PrPres or loss of signal and infectivity.

I just have one more comment relative to

Dr. Bailar's, that, yes, from the perspective of transmission, we are concerned about what is left over. I think that's clear. But from the perspective of trying to define the potential of methods or processes to reduce what's left over, we are left with measuring the magnitude of the capability of that method to inactivate prions.

Through long experience with viral validation, the only assurances we have are if we have a significant or large capability to inactivate. That is where this sort of 4 log number comes up that we all work with and you see in the literature.

So it's still, I think, very important to establish that a method has a capacity to inactivate or remove, in this case, prions relative to a process.

CHAIRPERSON PRIOLA: While still, in this case, maintaining the integrity of the device that is going to be reused.

DR. PETTEWAY: Exactly. I mean, if you destroy it or destroy a product -- and that's why I think the comments that have been made as we will never get to an absolute -- This is about doing our best that we can to minimize risk.

CHAIRPERSON PRIOLA: Thank you. I think that's really worth reemphasizing, that we can't get

to an absolute based upon what we have.

Are there any other comments on the first three questions by anyone? Dr. Wolfe?

DR. WOLFE: Just a comment on Dr. Weissmann's suggestion, which is that the beauty of the suggestion is that, by varying A, the surface area, and B, the metal that the spheres are made out of, you really could bridge the gap between some of these other experiments and things that at least more closely approximate the device that's going in there. So I think that that is a very fruitful thing to pursue in terms of (quote) "validation."

CHAIRPERSON PRIOLA: Shall we move on to question 4 then, which I think we have already -- I mean, we've touched on all of these during this discussion.

DR. WOLFE: I think we have discussed question 4 thoroughly, really. I doubt whether we can add anything else.

CHAIRPERSON PRIOLA: Yes, I think that's right. Are there any other comments or suggestions by members of the Committee? Anyone? Yes, my second question was going to be to the CDRH. Does the CDRH have any comments or requests?

DR. DURFOR: We would really like to thank

you. We recognize this has been a very challenging -- Oh, I'm sorry, Stan.

DR. BROWN: Considering question 4(a), one of the things we were trying to get at is the level of infectivity in terms of how far down -- We talked yesterday about brain spinal cord, maybe spinal column. We've talked about tonsils. We've talked about eyes.

From the types of tissue to which these instruments are exposed, can you give us any guidelines as to how far down the neurological tree we go before we stop worrying about TSE contamination? That's sort of the subtle little bit about that first part of 4(a).

CHAIRPERSON PRIOLA: The neurological tree?

DR. BROWN: You're talking about, you know, what nerve root level, optic nerve, auditory nerve. If we are doing a cochlear implant, we are connecting to the auditory nerve. We are doing eye surgery, we are getting the optic nerve. What neurological level do we begin to say we don't need to worry about contamination, because it's a low risk tissue?

So that's part of the matrix that David

Asher had with high risk tissue, low risk tissue, high risk patient, low risk patient. Is there any kind of guidance you can give us in terms of the level of tissue risk?

CHAIRPERSON PRIOLA: Right. Dr. Gambetti, do you want to address that question?

DR. GAMBETTI: While I have just a rule of the thumb, I would say from what we have seen, certainly, as far as I remember, everything that is inside the head, inside the cranial is considered to be high risk.

Then things that also are outside, as we learned recently, in addition to the remainder of the central nervous system like the spinal cord and the dorsal root ganglia. But in addition, also other things that are outside the cranium, like the olfactory epithelial, as we learned recently.

So as a rule of the thumb, I think everything that's inside the cranium, spinal cord, dorsal root ganglia, are at very high risk. Then depending on the form, other. As we know, lymphoreticular system in variant-CJD, is obviously also, and the GI tract also I would consider high risk. For sporadic instead, I think we are with all what is inside the cranium and possibly other tissue

directly connected with the central nervous system.

CHAIRPERSON PRIOLA: So you would agree -- Someone -- I'm sorry, I forget who -- presented that sort of list of decreasing risk.

DR. GAMBETTI: Goes from here to here, everything, and then down the spinal cord, dorsal ganglia in the sporadic form. In variant-CJD lymphoreticular system, GI tract, and perhaps even more that I am missing now.

CHAIRPERSON PRIOLA: Any other comments from the Committee? Dr. Stroncek.

DR. STRONCEK: You know, there's some -- There's been a lot of discussion about the need to keep instruments wet, contaminated instruments wet and material not drying out, and someone brought up the point that, well, maybe these solutions might be contaminated, too. But based on the fact that whatever the hospitals are doing now with these little solutions that instruments are put in, it's not causing any problems. We don't have to worry about disposal of the solutions that instruments are washed in, do we?

CHAIRPERSON PRIOLA: Well, I think you have to consider it, but I think also that is something that would be incorporated in any study that

is going to do this. If you have a rinse, you can check the rinse for infectivity.

I think you can never -- I know we certainly discount it in our lab. Dr. Durfor, would you like to comment?

DR. DURFOR: I would like to thank the Committee and all of the attendees here. This has been recognizably a very difficult area, and we didn't expect people to be able to give us all five fingers and say this, this and this. We wanted to hear your thoughts, and I think we did. I very much appreciate that.

I think the call for a forum of generally collecting people together to discuss everything from issues of assay development to clinical risk to clinical practice -- I think that's a very wise thing that we will have to seriously consider taking advantage of. So we want to thank the Committee very much.

CHAIRPERSON PRIOLA: Okay. If there are no other comments or questions, then we can adjourn for lunch, and return at 12:50.

(Whereupon, the foregoing matter went off the record at 12:06 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(12:59 p.m.)

CHAIRPERSON PRIOLA: If I could get the Committee members to sit down so that we could begin this session. Most of the people here have planes to catch. So we would like to get going.

Well, I think let's go ahead and get started. We have the majority of the Committee members here. The topic that we are going to discuss for this afternoon is actually in two parts, and the first part -- both of which actually overlap somewhat with what we were discussing this morning and yesterday, which is decontamination of equipment and facilities.

The first half deals with ocular tissues, and we are going to have Dr. Ruth Solomon discuss methods used to gather these tissues.

DR. SOLOMON: As mentioned, my topic does overlap with the topic presented by CDRH. As you may know, FDA has various centers. CDHR or the Center for Devices regulates medical devices such as surgical instruments or equipment.

The Center for Biologics, CBER, regulates tissue for transplantation. We regulate the eye banks and tissue banks which use the surgical instruments to

procure and process tissue.

Next slide, please. As I said, some of my slides you will have seen before, but I am going to review them in the context of human tissue for transplantation. Just to say at the beginning that, while FDA regulates human cells and tissues, another Federal agency, HRSA, regulates or oversees organ and bone marrow transplantation.

Okay. This is the chart that you have seen many times before in which the WHO classifies various organs and tissues into high, low and no detectable infectivity. Eye is considered a high infectivity tissue, and the WHO does not differentiate between the different parts of the eye.

Most of the tissues that CBER regulates fall into the "No Detectable Infectivity" category. Next slide.

This slide i snot in the handout. On the other hand, the CJD incidence panel uses the three categories of high, medium and low or no detectable infectivity, and they separate CJD from variant-CJD, and also they distinguish certain parts of the eye from other parts.

So for instance, retina -- and we could also add optic nerve -- is considered a tissue of high

infectivity for both CJD and v-CJD, but other ocular tissues such as cornea, sclera, lens, fall into the medium infectivity category for both CJD and v-CJD. Blood and other tissues fall into the low or no detectable infectivity category.

Next. My presentation is really a follow-up on a previous TSEAC meeting which was held on June 26th of last year. At that time, we asked the Committee to consider approaches to reduce the risk of TSE transmission by cells and tissues -- which we have an acronym -- HCT/P transplants.

At that time, we were concerned about the pooling of tissues from different donors, particularly bone tissue. So we presented three approaches, the first being to screen the donor for risk factors for and clinical evidence of TSE disease. The second was to control recovery and processing to prevent contamination, and the third was to use manufacturing steps that remove or inactivate TSE agents.

Next slide. We asked the Committee last year several questions and, as is not uncommon, the question about control of processing was not voted on, but rather the Committee reworded it and presented a charge to the FDA.

The charge that the Committee put forth

is: Do the Committee members recommend that FDA define validated inactivation procedures for TSE decontamination of instruments and surfaces, and propose methods for removal and/or inactivation of TSE agents from HCT/Ps that may be contaminated by TSE agents, differentiating high risk from low risk tissues?

Then the Committee proceeded to vote on their own question, and there was a unanimous YES vote.

Next slide, please. So this session is really a follow-up on trying to answer that question posed to us.

The U.K. CJD Incidence Panel Report describes TSE infectivity in ocular tissue. In studies with scrapie infected hamsters, if we considered the brain to have greater than 107 ID 50 per gram, they found that the optic nerve and retina had approximately the same level of infectivity as brain, but cornea, choroid and lens had -- could have three logs less infectivity.

They also discussed a patient with variant-CJD in which they compared level of PrPSc in brain, retina, optic nerve, and other parts of the eye. In the patient the retina had 25 percent of the

brain level, the optic nerve 2.5 percent. In all of the other ocular tissue there was no detectable PrPSc, and the level of detectability of the test would mean that there is less than 0.25 percent of the brain level.

There have been reported transmissions of TSE by tissue transplantation. There are numerous case reports of transmission by dura mater. The latest figure we have about the number of dura mater transplants per year is a '97 figure of 4500, but we think that that number has gone way down at this time.

Cornea: There are approximately 50,000 transplants per year worldwide with three cases reported. One was a definite case reported in the U.S. in 1974, and both the donor and recipient had autopsies at which spongiform changes consistent with CJD were seen.

Then this is a correction of what appears in the issue summary and some of the handouts. Other handouts were corrected by hands. There was a possible case in Japan in 1994, and the reason they called it possible is that, although the recipient had an autopsy consistent with CJD, there was no medical history and no autopsy performed on the donor.

Then in 1997 there was a probable case in

Germany in which an autopsy was performed on the donor. However, the slides were not available to confirm the diagnosis of spongiform encephalopathy consistent with CJD. The recipient also did not have an autopsy, but from the neurologic symptoms and EEG findings, her disease was consistent with CJD.

For other tissues, there are approximately more than 850,000 transplants per year, and no known cases of TSE transmission.

Next. Now I am briefly going to review the final rules, proposed rules, guidance, and draft guidance that FDA has in place concerning human cells and tissues for transplantation.

We have been regulating human tissues since 1993, and in 1997 the rule was finalized, and a guidance document accompanied it. But this rule was focused primarily on screening and testing of donors of musculoskeletal, skin and ocular tissue for HIV and hepatitis.

This rule does have one section which requires that eye and tissue establishments have validated procedures to prevent contamination and cross-contamination of tissues during processing, but there are no other GMP-like requirements in the 1997 final rule.

Since '97, we have been -- we put forth a proposed approach and have been implementing that with three rules. One of them has finalized the registration and listing rule. The other two are proposed and are in the process of being finalized.

A donor suitability rule, a proposed rule, was issued in '99, and it includes screening for TSE including CJD, and a proposed good tissue practice rule was issued in 2001.

Last year we published a guidance on validation to clarify our expectations of that one section in the 1997 final rule, and this guidance contained a statement that currently there are no validated methods for TSE -- to prevent TSE contamination and cross-contamination, but as validated methods become available, we would expect you to use them.

Also in the same year we came out with a draft guidance on CJD, vCJD, and that was presented to the Committee at the June 2002 meeting.

The discussion today will help FDA provide draft guidance that will accompany the GTP rule, once finalized, and the guidance would explain how to interpret some of these GTP requirements.

Next slide, please. Just briefly to show

you what is contained in the GTP proposed rule, these are GMP-like requirements, but unlike true GMP they just focus -- they are designed or focus on prevention of communicable disease transmission.

So, for instance, there are sections on facilities in which we would expect that contact surfaces are disinfected between donors, or some other method used to prevent contamination and cross-contamination; that equipment be cleaned and maintained, instruments decontaminated and sterilized as appropriate; supplies and reagents verified to meet specifications and not contaminated; that there would be tracking of which instruments, equipment and reagents were used in the processing of a particular HCT/P; and then the environment would be controlled and monitored.

Next, please. Then I'm just reviewing again the WHO Consultation. To start our, as we already heard, instruments should be kept moist after use, and they may be mechanically cleaned. But to answer some of the previous comments, I would like to mention that the WHO Consultation does say that, if you clean prior to TSE decontamination, the cleaning materials must be treated as infectious waste, and the cleaning station must undergo TSE decontamination.

Then as you know, the Consultation lists ineffective and sub-optimal decontamination methods and effective decontamination methods. It also discusses what to do with instruments based on the donor risk category and the particular tissue that the instrument has contacted.

So, for instance, in cases of confirmed or suspected TSE, high and low level infectivity tissues would require additional TSE decontamination. Tissues with no detectable infectivity would be routinely cleaned and disinfected.

Donors at risk of TSE, such as those that have received dura mater transplant or pituitary growth hormone -- For those donors, if the instrument contacted low or no detectable infectivity tissues, they would be routinely cleaned with no additional TSE decontamination. For high infectivity tissues and donors at risk for TSE, additional TSE decontamination is recommended.

Next, please. Then not to bore you too much, but this and the following slides go through the TSE decontamination methods mentioned in Annex 3 of the WHO recommendations, and they are in order of decreasing effectiveness and severity on the instrument.

So for instance, incineration should be used for all disposable instruments, and it is the preferred method for all instruments exposed to high infectivity tissues.

Next, please. Then if incineration is not practical, there are six methods listed for most effective to least effective, and notice that the decontamination is done first, and then the instrument is subject to routine sterilization.

The first five methods -- next, please -- involve either sodium hydroxide or sodium hypochlorite. The sixth method does not. It just says autoclave at 134 degrees C for 18 minutes.

Next, please. Then since we are also considering contact surfaces, the WHO recommends that for cleaning surfaces that you flood the surface with 2N sodium hydroxide or undiluted sodium hypochlorite for one hour and since with water, but if that is not possible, you thoroughly clean the surface and possibly use one of the partially effective methods.

Next, please. Then in the CJD Incidents Panel there is a detailed discussion of the number of decontamination cycles that an instrument undergoes. A decontamination cycle is defined as, first, physical cleaning such as in a mechanical washer, followed by

inactivation of any remaining infectious material -- for instance, by autoclaving.

The point to be made here is that it is the fist cleaning and the first autoclaving where significant decrease in infectivity occurs. Subsequent cleaning and subsequent autoclaving decreases infectivity by smaller amounts.

So, basically, the conclusion is that the first cleaning in autoclaving will remove -- will reduce infectivity at least 105-fold, and then a statement is made that most instruments that have undergone 10 decontamination cycles are unlikely to pose a significant risk.

Next. So in the context of ocular tissue for transplantation there are several other factors to consider other than what you have heard about so far. First of all, a risk assessment was presented at the June 2002 meeting, but it was emphasized that there are certain unknown variables in any risk assessment, and the two that particularly stand out and are applicable today are -- The two variables that we don't know much about are the extent of TSE agent reduction during processing and the extent of possible cross-contamination.

You should realize that one important risk

is having an insufficient supply or availability of evaluable tissue. Eye banks are considered small entities, and they have limited resources. So any recommendations -- That should be kept in mind when you make recommendations.

Also, the corrosive effect of sodium hydroxide and sodium hypochlorite on the longevity of stainless steel instruments used in procurement and processing of ocular tissue should be kept in mind.

Following me, the next speaker, Ellen Heck, will discuss the details of procurement and processing of ocular tissue and surgical instruments. However, I am going to quickly present the questions so you can keep them in the back of your mind as you hear that.

Next slide, please. There are four questions and, as Dr. Asher alluded to yesterday, basically the four scenarios are ocular tissue with a known TSE donor, ocular tissue where there is no suspected TSE -- that is, routine -- and non-ocular tissue, other low risk tissues when you have a donor with known or suspected TSE, and fourthly, low risk tissues where you do not suspect TSE, such as in the routine situation.

So all of these questions are prefaced by

this statement here, that you have to consider current practices using conventional methods of cleaning facility work surfaces, equipment, and instruments used in the recovery and processing of HCT/Ps.

You also should keep in mind the other precautions currently in place, which were discussed last year, such as donor screening for CJD and variant-CJD, also that aseptic techniques are used in procurement and processing of tissues, and third, concerns about availability or supply of tissues.

So keeping that in mind, the first question -- Next slide -- asks: With regard to the recovery and processing of ocular tissue from donors later discovered to have TSE or possible TSE, does the Committee believe that surgical instruments used in recovery and processing should be destroyed by incineration, if practical?

Next. If destruction of instruments is not practical, does the Committee believe that, at this time, there exist established, effective methods that are adequate for decontaminating instruments and surfaces?

Then if so, please comment on the specific methods listed in the WHO Guidelines. In particular, does the Committee consider that only those WHO

methods that use sodium hydroxide or sodium hypochlorite are adequate?

Next. If so, should such methods by employed by eye banks in the circumstances noted above?

E says: Does the Committee believe that the number of decontamination cycles -- again, a decontamination cycle is mechanical cleaning and autoclaving -- performed on the instrument after the index donor tissue was recovered and processed should determine whether or not additional specified TSE decontamination procedures are needed?

Then the second question, as I mentioned -- next slide -- is: With regard to ocular tissue, should we have additional TSE decontamination procedures used routinely, even when TSE has not been suspected in the donor?

Next. Should similar decontamination procedures be used for instruments and surfaces used to recover and process other tissues with a low risk of TSE infectivity from cases of known or suspected TSE?

Finally, these other tissues with a low risk -- should these additional decontamination procedures be used routinely, even when TSE is not

suspected? Thank you.

CHAIRPERSON PRIOLA: Thank you, Dr. Solomon. Our next speaker is Ms. Ellen Heck.

MS. HECK: Well, I thank you for the opportunity to come and talk to you today from one of those very small entities that Dr. Solomon referenced in her talk; because we are sort of a small entity in the greater world of science, and yet we feel like we have a place in it, in that we do try to restore sight to around 49,000 Americans each year. So we are very conscious of that responsibility.

Am I going to get slides or am I not? Okay. Oh, we're going to get them all at once. Okay.

First slide, please. Certainly, we are aware that we could have an increase or an outbreak, but we haven't had one in the United States since 1974.

Next slide, please. And we think that that is worth mentioning again. We could have a failure to detect a case by current screening. We know that not everyone is symptomatic. However, I think it is important to emphasize that we do, for the most part -- Over 90 percent of the tissue delivered in the United States is carefully screened by medical history screening questions.

Next slide, please. And these questions take in a combination of factors which help us to reduce those individuals who might be in a phase of symptomatic CJD, looking at memory loss, inappropriate responses, confusion, and certainly, motor changes. This helps us to eliminate a number of cases. We automatically defer anyone who is in this category.

Next slide, please. And in addition, we defer those patients with Alzheimer's, not because we think Alzheimer's is infective, but because we are afraid we might miss some diagnosis there or there is enough confusion about the diagnosis between Alzheimer's and CJD that we might inadvertently take a case.

We also look very carefully at any seizure disorder and brain tumors, or any neurological disorder, biochemical or otherwise, and this is where the eye bank's medical director plays a very large role in the screening process for us.

Next slide, please. So what do we have then in the processing safety for eye banks at the current time? Well, we have what I consider to be four things that are important as we look at what next steps may be appropriate for eye banking.

We have environmental control with a flow

hood, with our flow cleaning, with our barrier drapes, and I'm going to show you a little bit more about that in a moment.

Our graft isolation, I believe, is important, because there is no batching in eye banking. We do not process multiple samples at one time. All the processing is from one single donor, and it is in a limited quantity, and all of our grafts are for single patient use only.

Then, of course, we get to the sterile instruments where most of the emphasis has been through this meeting, and the aseptic techniques.

Next slide, please. We do a routine cleaning of our hood, and we do our in-laboratory incisions under a hood, but I want to make a differentiation for you. Hearing that we are just cleaning our hood for ambient contamination. We do not feel that our hood is ever necessarily contaminated with eye banking samples, and that is because --

Next slide, please. -- we are going to use barrier draping inside our hood, as well as the cleaning of the hood which took place before. We, of course, are wearing protective apparel, and as you can see here in the actual handling and removal of

corneas, we are not talking about a type of procedure where there is a great deal of residue or exudate or moisture or transmission or splatter. This is a very contained procedure. So there is limited contamination, and the barrier dressing that was under the hood then is going to be incinerated.

Next slide, please. What we do with our instruments is pretty much what you heard over and over today, to some extent. We do gross cleaning. We do moist transport. We do steam autoclaving. Then we go through recleaning, redisinfecting, packaging, and again some steam autoclaving.

I would like for you to just take a look at the size of these instruments. This, particularly with these scissors, will give you some idea about the delicate nature of these. We are not talking about large instruments that will withstand a lot of manipulation and a lot of treatment.

Next slide, please. For that reason, we have gone with the increased sterilization method. Again, I remind you, we do not normally consider these to be patients at risk for CJD. We don't take known cases. We don't take any symptomatic case, and so we don't feel like that we are, in large part, dealing with what you would consider someone who is at

potentially high risk for CJD.

We do, of course, realize that someone can slip through that even so. So we go ahead with the increased sterilization, which is not without some compromise even then to our instruments and our equipment. We've found that our equipment breaks down a little bit more readily when we are sterilizing at this high temperatures, and we have had to have it serviced a little more frequently, but that's a reasonable expectation and cost to assume.

Our instruments get dull a lot faster, about four times as fast as they do when we use the 121 for 30 minutes, but that, too, can be reasonable.

Next slide, please. We are concerned about the reasonableness of this, because eye banks are not sophisticated laboratories. We don't have the same facilities as a hospital decontamination unit or a research laboratory. So handling caustic chemicals is a risk to our personnel that we are quite concerned about.

Next slide, please. And with the sodium hypochlorite, we are very concerned about our instruments, because our instruments' sharpness is a big factor in the effectiveness of using sterilizable instruments.

It's not just whether you can see corrosion on the surface, but whether or not the instrument remains sharp enough to do the excision in a manner that renders the corner maximally effective for the surgeon when he punches his corneal button at the time of surgery.

Next slide, please. So I wanted to look at some of the cost factors that might be involved with other types of considerations. To do this, we wanted to break down the eye donor population in the United States by categories of age, since we've been hearing some concern that the age from 55 to 65 or maybe from 55 to 70 is the age range that you are most interested in, or maybe 60 to 70.

So as you can see, these are our primary donor categories. That's where the most of our tissue comes in.

Next slide, please. And our current sterilization protocols with some attrition of instruments built in gives us a cost per year in the over-60 age range of $247,000-plus . If you go down to 40, you've got 400, if you use only one set. Many of use two sets, because we are interested in controlling any microbiological cross-contamination from one eye to another. So the number of instrument

sets is doubled.

So in those figures, you would say that, to use the sterilization at this figure for all of the instrument sets used in the United States in the past year, our instrument cost -- sterilization cost was about $1 million.

Next slide, please. Now we are looking at disposable instruments, but disposable instruments have a couple of limitations which we have not yet overcome. They are not as precise or of high quality as our currently stainless steel instruments. So we do have some surgical compromise in getting the corneal button removed, but we can -- we are still exploring this.

The other limitation we have right now is that there is not a quality supplier who can at present provide enough instrument sets to meet all of the need if we were to go to even just above the age of 40. If we say, well, we don't worry about the ones below 40, but we are going to use disposable instruments for every donor above 40, right now that supply is not available.

Next slide, please. In addition, we take on some fairly significant added cost when we do that. If you remember, in the first slide I told you our

cost was about a million dollars.

If we used disposable instruments for all of the donors currently in the United States, we are looking at something around $4 million. So it is a significant increase in cost when we are not quite sure what our increased risk is or what we are actually preventing.

Next slide, please. That just goes over the differences. It's a $3 million difference, if we do it for everything. If we do it only above the age of 60, it's somewhere between nearly $800,000 and $1.5 million.

Next slide, please. So we have, we believe, some current safeguards in place which we are anxious to hear your comments on and to see what you think we can do that will improve these. But we feel like that this is a major component of our safety, is our screening and asking the appropriate questions, and rejecting those individuals who may have a suspicion of having a transmissible spongiform encephalopathy.

We think that our environmental control is relatively good, because we have a contained area, and we do not have contamination within the surfaces that we use. We do use disposables and incinerate the

drapes to contain that, and disposable personal protective apparel.

Our grafts are isolated. So the numbers of exposures would be limited. And finally, we are looking at ways to deal with the decontamination and sterilization, but we feel like adding the moist transport, the mechanical washing of these solutions, and then the sterilization seems to be adequate for what is known right now.

Final slide, please. You have a lot of things to consider, and I'm glad it's you and not me, because if nothing else, it's reconvinced me today I don't want any CJD. I never did. I'm sure of it now, but I do want to be able to continue to meet the needs of those 49,000 people who want corneal transplants and will not be able to see without them.

Thank you very much.

CHAIRPERSON PRIOLA: Thank you, Ms. Heck. Are there any questions for Ms. Heck from the Committee? Yes, Dr. Bracey?

DR. BRACEY: Yes. You stated that you defer greater than 90 percent of the donors by history. I guess my question is why not 100 percent?

Then following up on that, in the world of blood banking, you know, often the medical directors

will have to make some decisions. But those decisions are becoming more and more limited in order to promote uniformity in selection. I wonder, do you have uniform criteria for screening?

MS. HECK: Yes, sir. Well, to answer your first question, there are still some states, my state being one of them, who have a law called the Medical Examiner's Law that permits the medical examiner to release tissue to an eye bank without consent of next of kin, if there is no known objection.

In such cases then, there is no medical/social history interview, because there is no interaction with the family. We personally do not utilize that law and have not for over a decade. It is still used, however, by a very small percentage of eye banks across the country. That is something, certainly, for the Committee to consider.

Most of us have gone away from it, because we feel that, although not 100 percent reliable, a medical/social history does give us an extra degree of safety and should be employed.

The second question: We do have standards promulgated by the Eye Bank Association of American under which we screen. We use a 40 -- I think it's 47 questions now, which are very similar to the ones that

you do in blood banking as part of that screening.

The medical director's role is primarily to help us evaluate things that are uncovered either during that screening or in evaluation of the medical chart where we feel like our technical expertise is not sufficient and that we need to get the medical background involved.

DR. BRACEY: I would only comment that I would agree with you that that gap needs to be closed, as far as the history piece.

CHAIRPERSON PRIOLA: Dr. Hogan.

DR. HOGAN: Since its inception, this issue about records has begun. That gap has closed. Used to be a lot more eye banks that were utilizing medical examiner tissue. So that is decreasing over time. However, I should point out that the majority of medical examiner eye tissue comes from accident victims that are young. That is under the age of 40.

So there are decreased risks for sporadic CJD, and there are much better cornea donor -- corneas that are a lot better. So it's a problem of getting rid of that population, although it is gradually going.

MS. HECK: But, Dr. Hogan, if I may, we do take tissue from medical examiners' cases. We simply

approach the family for consent. So the issue would be the percentage that was lost due to decline from the family, not the percentage of losing all of the tissue under the age of 40.

CHAIRPERSON PRIOLA: Dr. Bailar.

DR. BAILAR: How many corneas per year would you need in a steady state? That is, if there were no backlog, how many new needs do you have coming up per year?

MS. HECK: We transplant approximately the same number of corneas for the last three to five years, and that has been fairly steady at around 49-50,000 corneas. Now one of the things that we are not in a position to evaluate right now, and certainly may have impact on what we are going to need, is the high degree of refractive surgery that is going on in this country today with all of the laser surgery that is being performed.

We may see two things happen. We may see some corneal failures as a result of the surgeries, which will make them need transplants, and we will certainly see a large number of individuals who would have been able to be considered as cornea donors not being able to be so considered.

DR. HOGAN: And I would like to point out

that there are 2 million Lasik procedures done each year, and that is growing as the cost comes down.

MS. HECK: So that's a real risk to our tissue supply.

CHAIRPERSON PRIOLA: Okay, thank you, Ms. Heck.

MS. HECK: Thank you.

DR. BAILAR: Can I ask one other question?

CHAIRPERSON PRIOLA: Oh, sure.

DR. BAILAR: What is the total cost of the procedure of collecting the tissue and of putting it into a patient, the initial workup, the follow-up and so forth? How do these costs of $20 to $50 fit into the total?

MS. HECK: The total cost of the delivery of a cornea now probably averages around $1800. There are lots of things that figure into the cost, and every time we have to add a new test or a new procedure, then that cost does go up. But I think we have to do education, we have to do -- We have to have a 24/7 staff. We have to have trained people. We have to have instruments, etcetera. So it's about $1800.

DR. BAILAR: That is to collect and prepare the tissue?

MS. HECK: Yes, sir.

DR. BAILAR: How about the cost of putting it in?

MS. HECK: It's running, I think, around another $2000. So the whole thing comes out to be a fairly bargain in the way of surgery in today's world.

CHAIRPERSON PRIOLA: Okay. Our next speaker is Dr. Dorothy Scott, who is going to present the second part of Topic 4, which has to do with plasma derivatives.

DR. SCOTT: So now we are switching from a high risk tissue to what you might call a lower risk tissue, which is blood and plasma, in particular today, plasma derivatives. The issue is the cleaning procedures, the clearance of TSE agents during manufacturing.

The concern that we are asking you to address is the use of common equipment for manufacturing of U.S. and European plasma for plasma derivatives in the context of variant-CJD risk.

Just to set out the issue in detail, many manufacturers use common equipment to process U.S. and European plasma, and they are approved to do so as part of their license or their licensing supplements. These products include plasma derivatives such as

immune globulin, albumin, FactorVIII and FactorIX.

At least five major manufacturers of plasma derivatives are licensed to use common equipment and facilities for U.S. and European plasma. However, the donor deferrals, the plasma and blood donor deferrals, differ between the U.S. and European countries. So in theory the level of risk may be slightly different.

I am just going to show you these donor deferrals in the next slide. Here you can see where the differences lie. These are the U.S. donor deferrals for source plasma and recovered plasma.

There is a difference that I can go into, but it is basically for technical reasons that the U.S. recovered plasma has a donor deferral for Europe from 1980 to the present of five years. It's not that we think it is any less safe than source plasma. It's more a matter of differentiating -- Getting a unit of blood and separating it into a suitable and unsuitable component is very complicated.

The main place where these donor deferrals differ between U.S. and Europe is in the deferral of people who have lived in the United Kingdom between 1980 and 1996, the higher risk period for being exposed to BSE. Our deferrals are for three months or

more.

In Europe and the various European countries it's between zero and five years, but typically it is six months for most countries.

In February of this year, the European Agency for the Evaluation of Medicinal Products recommended that at least a one-year deferral go into effect for the European countries, although they may be more stringent than that.

Again, we defer people who have lived in France for five years or longer. This usually isn't done in most European countries, and the EMEA is not recommending this. Of course, the Europeans don't defer European plasma. That, naturally, would not be recommended.

So you can see, these are where the differences lie. Can I have the next slide?

I just want to point out that the European risk of coming down with variant-CJD continues to appear to be low, and that is because they have a small BSE epidemic relative to the United Kingdom. Here, we perceive the French risk as being somewhat higher due to the greater number of v-CJD cases they have had, which is probably due to the import of British beef and beef products, especially into

France.

Next slide. So when you consider evaluating the risk of TSE transmission through reused equipment and materials, there are a couple of things which make this somewhat different from some of the other scenarios that you have looked at, such as tissues and surgery.

The amount of the agent in the starting material, which is plasma, is believed to be low, if it is present at all. So you are looking at low risk tissue instead of higher risk tissue.

In addition to that, there is a high likelihood that the people who are most risk even in Europe would be deferred because of people who have lived in the United Kingdom for extended periods of time. In addition, there can be clearance of the TSE agents. At least this has been experimentally shown for a number of the manufacturing processes.

The evaluation of cleaning procedures for potential chemical inactivation of TSE agents needs to consider these other influences on the overall risk.

Next slide. Still there is a possibility that cross-contamination could occur. That is, that a facility may process some potential -- well, some actually infected plasma, and that the donor would be

diagnosed too late to be able to interdict the use of the plasma or the plasma derivative.

In addition, I would like to point out that there still is a possible unpredictability when it comes to human TSE outbreaks. For example, we know that more BSE countries continue to be identified. Every time this Committee meets, some other country usually has been added to the list of BSE countries. Most recently, it has been Canada.

Also, there is a concern that people who are heterozygotes at codon 129 of the prion protein -- that is, methionine valine heterozygotes -- could develop vCJD but have a longer incubation period. This is just a theoretical concern, but it would increase the epidemic size and the number of people who come down with this disease, if it happens.

I would like to point out, but not to emphasize, that we do have chronic wasting disease of deer and elk in the U.S., and that the spread to humans or domestic animals is not impossible. We think it isn't too likely, because the -- well, for a number of reasons that I won't go into now.

I would like to point out that decontamination of facility, equipment and enhancement of safety, if possible, is analogous to the importance

of continuing food chain controls, in that if the BSE epidemic finally worldwide loses steam, and it seems to be losing steam in most countries, would we stop having food chain controls or would we continue a certain level of prophylactic -- give some prophylactic attention to the possibility that this could happen again?

I think that, when we consider this, even if we think there is a low risk of contamination, we don't always know what is coming next. So it is still a useful thing to consider.

Next slide. This is just to point out that Canada now, even though in this August 2002 website, which is still up, was listed as a Category II, just like the U.S., for BSE. Of course, now it's moved into Category III. So it is not entirely predictable where BSE will occur next and where human exposures could occur next.

Next slide. This is just to show you that the epidemic of vCJD in the United Kingdom finally appears to be waning, and this is just -- It's all from the same paper, and this is looking at all deaths from vCJD and, statistically speaking now, these are believed to be going down, presumably as a result of the food chain controls that were instituted in 1996.

Next slide. This is just a list of the vCJD cases in Europe, and many of these people were not exposed to -- or did not live or travel to the United Kingdom in the past. This case has not been confirmed. It's just been reported in the press, and it is still being worked up.

Just to point out, therefore, that a post-donation diagnosis of variant-CJD in a European donor is possible where plasma derivatives may have been processed.

Next slide. I just want to mention a few additional factors to consider in more detail. That is that we believe there is infectivity clearance -- at least experimentally, it has been shown -- during plasma derivative manufacturing.

The common manufacturing steps that can result in TSE clearance include many precipitations, certain depth filtrations, and column chromatography. Clearance, as is the case for many of the other situations that you have looked at today, is process and manufacture-specific, because it is context-specific.

As most of you who are here recall, we invited manufacturers to submit clearance data for their specific processes to us for consideration of

labeling claims about TSE clearance in the last meeting in December of 2003.

Next slide. Now I just want to briefly mention, and you will hear an additional presentation about this from the Plasma Protein Therapeutics Association, the cleaning procedures that are typical between plasma batches, which are called campaigns.

Validation of equipment cleaning procedures is standard for licensure, but this validation is not TSE-specific. Examples of cleaning methods that are commonly used are cleaning of stainless steel tanks, for example, with sodium hydroxide solutions or hypochlorite solutions, as well as extensive rinsing.

Examples of typical cleaning validation test methods that are used and specifically requested for licensure are testing for residual total organic carbon, testing for residual protein, and also testing the ionic strength of final rinsing solutions. These are just examples, but they will be common ones.

Next. Just to give you an idea of what equipment and materials might be reused or might not be reused in a plasma manufacturing facility, usually these are reused after cleaning: Plasma pooling equipment; stainless steel tanks; tangential flow

filters; gaskets and tubing, and there's been a lot of discussion about nooks and crannies and, certain, this is where you may find nooks and crannies -- we know from other people's experience that it would be extremely arduous and difficult and take a long time to remove and replace all your gaskets and tubing in between plasma campaigns; sterile filtration and final filling machinery; affinity chromatography columns; and some other resins.

Things that are usually disposable and are usually disposed of between plasma campaigns are sterile filters, depth filters, and some resins, especially resins that are used for adsorption.

I also want to point out that, in the case of U.S. licensed products, we typically request that items such as tangential flow filters and affinity chromatography columns be dedicated for U.S. plasma.

Next slide. Just very briefly, I want to talk about chromatographic column retention of TSE infectivity, which is a concern that we have, and we understand that the industry is addressing or beginning to address this concern as well, from Dr. Kempf's presentation this morning.

This is one of the very few published studies of plasma derivative processing by Peter

Foster from the Scottish National Blood Transfusion Service in Vox Sang. Here he looked at scaled down manufacturing processes. So it was a validation style study.

He looked at various resins that are used in their manufacturing of thrombin, FactorIX. He also looked at a number of other plasma derivatives, but these did not happen to have these kinds of resins for this purpose.

So here I have listed what the resin was, and it so happens that we have a cation exchange resin, an anion exchange resin, and a Heparin-sepharose column, which is a type of affinity column. These are just -- The products are intermediates that these resins are used to produce.

These are the reduction factor of PrPres that you see here in logs, and the reduction factor is the titer of the spiked intermediate over the titer of the resultant fraction. Here you see that the cation and anion exchange columns both retained a substantial amount of PrPres. There were not infectivity studies done as part of this particular work, and Heparin-sepharose, for some reason, a bit less.

Next slide. Dr. Foster commented that only a small proportion of PrPsc -- I said PrPres, but

anyway he did use the hamster model, I believe -- could be accounted for in samples taken over chromatographic procedures, e.g. about 0.1 percent.

What he is saying here is that you can elute everything, and you do not have mass balance. The probability that most PrPsc remained bound to chromatographic matrices emphasizes the importance of either limiting the reuse of adsorbents or in developing suitable cleaning procedures.

Next slide. This has been demonstrated in other studies that actually use scrapie infectivity. However, they did not study the particular processes that are used for plasma derivatives. But these also looked at anion and cation exchange columns, hydrophobic interaction columns, and affinity chromatography, and typically found that between 102 to 105 logs infectivity were retained by such resins.

I would also like to point out that some chromatographic resins, like anion and cation exchange columns, are fairly robust with respect to alkaline conditions, and they can actually tolerate 0.1 to 1 molar sodium hydroxide. But there are others which cannot, because they do not remain chemically stable, particularly the affinity columns and the hydrophobic interaction columns.

Next slide. So I am coming close to the questions, which I will introduce now, and then you will be looking at them again later after the last two presentations. Again, I just want to emphasize that we are asking you to consider the overall context of this risk, and that includes the amount of agent present in the starting material -- the amount of TSE infectivity in plasma is believed to be low, if it is present at all, has not been demonstrated -- and that deferral of at-risk donors from the U.K., in particular, limit the number of possible incubating donors that will be contributing to a plasma pool.

In addition, we do have evidence for clearance by manufacturing processes, and this has been demonstrated in general for many common procedures used in plasma derivative manufacturing. But submission of rigorous and process-specific studies has been requested by FDA on a voluntary basis. We have some of these. We certainly don't have all of these.

Next slide. I am just going to introduce the questions. There are only two, you'll be glad to know. The first question, which you might feel better able to give an answer to after the next presentation, is whether current facility cleaning methods, e.g. the

use of solutions of sodium hydroxide or sodium hypochlorite followed by extensive rinsing cycles, are adequate to minimize the possibility that an infectious dose of the vCJD agent may be carried over from one manufactured lot into the next.

Now I realize that I am not showing you today all of the things that are done in all of the facilities for all the products. So you may find this a difficult question to answer in detail.

Next slide. The second question is somewhat like some of your other questions. That is, are the available scientific data sufficient for FDA to recommend specific methods for cleaning of equipment used in the manufacture of plasma derivatives with respect to TSE clearance or inactivation?

So we are talking about the information that you have in your papers, your statements, and the information that you have seen in all of the introductory lectures or, I should say, presentations.

If the answer to this question is yes, please identify which methods can be recommended. If the answer is no, please describe what additional studies might assist in development of such recommendations.

Next slide. The following two talks are relevant to this issue. Dr. Cristoph Kempf will be back, this time to talk about typical decontamination practices for plasma product facilities, not in reference to TSE but basically what is already being done.

Finally, we will hear about a proposed PPTA-sponsored collaborative study on inactivation of TSE agents with sodium hydroxide and sodium hypochlorite. Thank you very much.

CHAIRPERSON PRIOLA: Okay, thank you, Dr. Scott. Are there any questions for Dr. Scott from the Committee? Okay, thank you very much.

We will move on to the next talk, which is Dr. Kempf.

DR. KEMPF: Thank you. Now as we have heard, validation is a common procedure, cleaning validation that has to be done on the equipment. However, pathogen-specific validation has several hurdles. May I have the next slide, please.

It appears that it has to be done if we want to do validations on a downscale level, like it has to be done with virus validations on the process, which would mean the cleaning process has to be scaled down. This, in most cases, is absolutely impossible.

Physics does not allow it, because rheologic properties are different on a small scale compared to a large scale.

If you would compare a 3,000 liter tank, and you would like to scale down as to 1 liter tank or pipings with one-inch or two-inch diameter to one millimeter diameter, there is no way you can do this, and also detection limits from current methods are way too high to be meaningful.

In the next slide, you just want to illustrate here that downscaling is not always possible due to rheological properties.

Also, the detection limits -- If you want to study inactivation or removal in a cleaning relevant way, it would be necessary to be able to detect something like 10-3 infectious units per square millimeter of surface, which would correspond to about 100 molecules of the surrogate marker PrPsc.

Next slide, please. Now what is currently done, and what do we use? We use cleaning and sanitizing solutions, several commercial brands. I just would like to highlight that in most of them you have alkali sodium hydroxide or you have active chlorine in it or you have a combination of sodium hydroxide and sodium hypochlorite.

So the two most frequently -- next slide, please -- used active ingredients are sodium hydroxide, and this varies between 0.05 to 1 molar. Temperatures used in cleaning procedures, they go from 4 degrees up to 65, and can be as short as 10 minutes or go up to several hours in the case mainly of chromatographic columns, which sometimes is stored in sodium hydroxide solutions.

Sodium hypochlorite is used between 100 and 1,000 ppm, from ambient temperatures to 45 degrees, and durations from one up to 30 minutes.

Next slide, please. Now cleaning usually consists of a prerinsing with tap water followed by a sanitization either with sodium hydroxide or sodium hypochlorite or a combination presence of detergent using this commercially available solutions that I just showed. That is routinely done between each batch.

Cleaning validation is performed on the product on contact equipment, and it is done in a way that the residual total organic carbon is determined on the swab samples. Swab samples are taken before and after the cleaning procedure.

Next slide, please, which shows you a few examples, what is used in chromatographic columns,

sodium hydroxide from 0.51 molar, 22 degrees for 60; tanks usually from 0.1 molar, cleaning in place, or ultra filters from also 0.1 molar up at ambient temperatures, and cleaning in place, as high as 80 degrees or 60 degrees with sodium hydroxide.

Next slide, please. Again, here are typical cleaning in place procedure. You first rinse with tap water. then you go with 0.15 molar sodium hydroxide, 40 degrees, again tap water. Then you use phosphoric acid, distilled water, and you rinse with water for injection at 80 degrees.

The next slide, please. If you performed the cleaning validation after such cleaning in place procedures, those are the typical results that you get. Precleaning, you can detect total organic carbon, and post-cleaning you are usually down at the detection limit. In our case, this is less than 266 parts per million. That's from a swab sample from 100 square centimeters.

So you can calculate the reduction factor, which is approximately 1000-fold or 3 log. We have yesterday that in some cases it can show cleaning -- or reduction by cleaning up to 4.5 logs. It might be more. It just depends how dirty you make your initial start, if you come down to this.

The detection limit is placed on environmental samples taken outside the tank or from blank -- based on TSE results of the blank. Next slide, please.

If you transform this to manufacturing process and look what this cleaning validations may tell you concerning batch to batch segregation, we have to make assumptions, and I would like to carry you through some theoretical considerations.

If you take a process like IVIg production, you can separate this process into different modules. Each module, as we already heard from Dr. Scott, was also evaluated on its ability to reduce TSE agent. I am talking about the manufacturing process and reduction of TSE agent by different manufacturing steps.

So that's the process, how we can divide it. Next slide, please. You have to make a few assumptions and look at a few facts. We take that the cleaning process, according to the total organic carbon values we obtained from cleaning validation, reduces the load by 3 logs. This reduction applies proportional to proteins, including the TSE agent.

Next slide, please. Now if you assume that a production pool would be contaminated with a

vCJD donation with one signal, the total load of TSE agent would be on the order of 5,000 infectious units or 3.7 log. This is based on the estimation by Brown that, if any TSE agent would be present in a deceased person, it would not exceed 20 infectious units per ml.

All TSE agents adhere to the surface of module one in the production process. We cannot simulate ways in between. So we have to take the capacity that the process has to reduce TSE coming to the final product or we have to assume that 100 percent goes -- sticks to the first module and does not go three. Everything in between, we have no values that we could model this situation.

Next slide, please. Then we would have this situation. This vCJD donation would go in the pool into the first module, leave behind 3.7 log. In the next batch there is a cleaning in between. It would be carryover to the second module, but due to the cleaning, it was reduced by 3 log. So we can carry this on over this five different modules, which leaves us at the end with a number that is -8.3 log that would go into the final product of a given batch.

Next slide, please. Now if we take these values that I just explained and take 2000 liter

plasma pool, which results in about 8,000 grams of IVIg, it would be 3.9 log. Then we would have a theoretical residual amount of -12.2 log or about 6.3 times 10-13 per gram of IgG.

Now if we -- We should not forget that these theoretical calculations or these assumptions, they do not take in account any inactivation that will occur by the use of sodium hydroxide or hypochlorite or any other sanitizing agent.

Next slide, please, which leaves me with the conclusion: We believe that the existing processes in place provide adequate safety to prevent cross-contamination from one batch to another batch, which means with the current procedures we have a full batch to batch segregation.

Also, I would remind you what I showed this morning and we heard also yesterday, that commonly used sanitization fluids such as sodium hydroxide or hypochlorite demonstrate the destruction of the pathogenic agent, TSE. I thank you for your attention.

CHAIRPERSON PRIOLA: Thank you, Dr. Kempf. Are there any questions from the Committee for Dr. Kempf? Thank you very much.

Our final speaker is Dr. Andrew Bailey.

DR. BAILEY: Okay, I'd like to thank the Committee for the opportunity to present to you a study which is nearing implementation phase, which is a study which will be sponsored by the various member companies of the PPTA and organized through the PPTA. So first slide, please.

So this study will be an investigation of sodium hydroxide and sodium hypochlorite, but the study will attempt to be quite a comprehensive investigation of the inactivation of a mobile TSE agent using these two commonly used sanitization agents.

Next slide, please. So the purpose of the study is to look at the influence of various factors like the concentration of the agent, temperature, time, on the effectiveness of TSE inactivation and, from that, to establish a database of inactivation data which can then be used for more company-specific cleaning and sanitization studies for removal of prion agents.

Next slide, please. I think it is important to emphasize again the cleaning and sanitization is a two-stage process, and that prior to sanitization the equipment is cleaned either by rinsing with solutions containing or without

detergents in order to remove residual protein, lipid, etcetera.

That is an important stage, because by reducing the effective protein load for a number of these sanitization agents, you improve the efficacy and the robustness of the inactivation potential by these particular agents.

Next slide, please. So why have we selected hypochlorites and sodium hydroxide? Really, these are two of the most commonly used sanitization agents within industry. So as a starting point, these appear to be the most effective ones to select, and there is some data already available which I will show you in the next slides which support that these agents do have a capacity to inactivate prions.

Firstly with hypochlorites, generally just looking at its mechanism, it is an agent which is highly reactive against all protein material. It results in modification of proteins, hydrolysis of the peptide bonds, and as I've indicated, already has some demonstrated potential for prion inactivation.

Next slide, please. Hydroxide -- we probably have a more extensive database, and already with viruses we know that at concentrations of 0.1 molar outputs, it is effective for virus inactivation.

The mechanism is, to a certain extent, understood, and it involves both protein denaturation as well as a more slower hydrolysis of the protein to break the protein up, and there is data also for this reagent that it is effective against the TSE agents.

Next slide, please. Now this is a table which just summarizes a large proportion of the available data we have for hydroxide, and it shows increasing concentrations of hydroxide as you go down the table, different strains of agent which were used in these studies, and some of the conditions.

What you can see from this table is that, really, a comprehensive picture or a conclusive picture of what conditions yield complete inactivation is not very clear to see. There are some conditions at lower concentrations where you get complete inactivation, other ones even at quite high concentrations where you don't get complete inactivation. It doesn't appear to be related to strain.

So we have here basically a dataset which is quite difficult to get a clear interpretation.

Next slide, please. Very much the same is true for hypochlorites, and there are some conditions at quite low concentrations which have yielded

complete inactivation of the prion agent, others which have not yielded complete inactivation. So a similar picture emerges there.

Next slide, please. Before I get into the actual study, I would just like to present some considerations which, I think, Bob Rohwer actually presented in quite some detail yesterday.

That is that, with the kinetics of inactivation, it is important to consider that these kinetics tend to be biphasic. You tend to have a very rapid initial rate of inactivation, and this is followed by a more slower rate of inactivation for residual infectivity.

This is true both for viruses and for TSEs. We have seen similar behavior, for example, with parvoviruses with inactivation by hydroxide. The aim of the industry study really is to try and investigate both of these phases to get a better understanding of the initial kinetics and the slower phase inactivation as well.

Next slide, please. So getting into the study design, we will be using the 263 Hamster scrapie strain. This is a model that's been extensively used in other TSE studies. It has a validated Western blot assay available to look at the surrogate marker for

prion PrPres or PrPsc, and also it is quite easy to do confirmation of these studies by bioassay.

The slide material we will be using will be a 10 percent brain homogenate, but what is still under discussion is the final concentration of brain homogenate that will be present in the inactivation solutions.

As I presented on the previous slide, the protein load by the time you get to sanitization is probably quite low, and we want to make sure that that is adequately modeled in the study.

Next slide, please. So this just tabularizes the various conditions that we are looking to investigate in the study. For both hydroxide and hypochlorite, we are looking to investigate three different concentrations of the reagent, covering the most commonly used concentrations used within industry.

Three different temperatures will be investigated, and for the various conditions we are looking to analyze samples with different time points following inactivation in order to try and get a better understanding of the kinetics.

Now although every box here on the table is taped, the samples where we are selecting for

titration will depend on results from the modular approach to the study, and I will outline this modular approach in the following slides.

Next slide, please. So the first stage of the study will be a Western blot investigation of the initial inactivation kinetics. This will be performed using the least stringent conditions, i.e. the lowest concentrations of either hydroxide or hypochlorite at the lower temperatures.

The reason we are selecting these is you saw some data earlier today which indicated that already at these lower concentrations we see a very rapid loss of PrPsc signal in the Western blot assay. So, really, if we can establish that at the least stringent concentration of reagent, least stringent conditions, then we can reasonably expect that under the more stringent conditions we are going to have equivalent rates of inactivation, if not slightly better.

The second stage of the assay will be a confirmation in animal bioassay. This will serve to confirm some of the initial inactivation kinetics that we observed with the Western blot studies, but also to look at a determination of the final inactivation potential after extended incubation periods, maybe of

30 to 60 minutes.

Next slide, please. So in terms of the Western blot studies, as I've indicated, we already have data that, at these least stringent concentrations of reagents, we already have rapid loss of signal, and this will be confirmed prior to proceeding to the bioassay.

As I've indicated, once we have demonstrated that we do have this initial rapid loss of signal, we are not going to proceed with any further Western blot investigations under more stringent inactivation conditions.

Next slide, please. The bioassay experiments, preliminary experiments will be performed to determine the toxicity of the samples prior to titration so that we can determine the appropriate dilution that we can use for titration.

The samples that will be analyzed will be analyzed by serial dilution, so that we can precisely identify the titer of the remaining residual prion in the samples. This will not be a study aimed only at determining whether we get complete inactivation or not, but we are looking to determine the actual titer of scrapie in each of the samples.

Next slide, please. Once we have

confirmed the initial kinetics, rapid kinetics of inactivation in the bioassay, the aim is to -- with select additional samples from the more extended time points, 15, 30 or 60 minutes -- As I've already indicated, we would not expect to see significant differences in the initial phase -- initial kinetics of inactivation. But what we would be looking to do is, with extended conditions, maybe with more stringent concentrations of the reagent or stringent conditions for inactivation, say, at higher temperatures, try to identify conditions which maybe would lead to complete inactivation of the prion reagent.

One of the things we will try and incorporate into the study, and this is something that has been the subject of discussion for some years, is the possibility of extended observation times of some of the animals. What has sometimes been observed is following treatment with hydroxide that you can extend the incubation period for the disease, and we are looking to possibly investigate that by extended observation of the animals out beyond, say, the normal 200-day incubation period that you would use for the hamster animal bioassay.

So the final slide, please. So just to

conclude, the study will contribute, we believe, quite significantly to our current understanding of how factors like temperature, concentration, and time impact on the inactivation of these agents by sodium hydroxide and hypochlorite.

It will allow correlation of the Western blot versus the bioassay for the use of the Western blot in inactivation titer studies. This is something that was discussed earlier in some of the roundtable committee discussions. So that will certainly contribute to our understanding of how good PrPsc is as a surrogate marker for prion inactivation studies.

Finally, it will provide a solid basis for the companies to go on and do more company-specific cleaning studies, maybe combined cleaning with sanitization, which is then the ideal model, I think, for the kind of cleaning and sanitization procedures that we use routinely for our plasma products.

So thank you for your attention.

CHAIRPERSON PRIOLA: Thank you, Dr. Bailey. Are there any questions from the Committee for Dr. Bailey? Oh, Dr. Gambetti.

DR. GAMBETTI: Just a quick question. Why do you use Western blot for detection, since there are claims that ELISA is probably more sensitive in

detecting PrPsc? In other words, I would try to use the detection method that is the most sensitive available, so you can actually compare that detection with the bioassay.

DR. BAILEY: We have a lot of history with the Western blot. It's been used for prion removal studies or the plasma manufacturing processes. So that was one of the reasons in considering it. But one of the nice things about the Western blot when you compare it, for example, with the ELISA is that, when you have a signal, it is very diagnostic and easy to interpret with the Western blot; because you have a band in a very specific position in terms of its molecular weight, which you don't always have that high level of confidence with the ELISA assay, for example.

My understanding is that the difference in sensitivity between the assays is not so great that it would significantly impact on what we are trying to do here in terms of look at the initial inactivation kinetics with the Western blot. But really, the bioassay, I think, is going to give us the most comprehensive datasets.

The investigations with Western blot really are just to allow us to identify what the most

appropriate conditions would be to go in with in the bioassay system. From an ethical standpoint, there are considerations there that we can reduce the number of animals that we need to use in these kind of bioassay systems, which has constantly been encouraged by the ethical committees.

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: How did you pick these particular concentrations, given that you could certainly have gone lower and, I presume, could have gone a bit higher?

DR. BAILEY: These are routinely the kinds of concentrations that are used in manufacturing procedures. So they were selected based on information gathered from the various member companies.

DR. BAILAR: So in the end, you can look at what is now being done?

DR. BAILEY: Yes.

DR. BAILAR: But you would have to gather additional data if you wanted to look at possible other concentrations outside this range?

DR. BAILEY: Yes. I mean, we had to start somewhere, and this seemed the best place to start. But, yes, if the data we get from this doesn't

demonstrate that some of these conditions are effective, then we may need to do additional work.

DR. BAILAR: I think that is fine to start with this, as long as you recognize that you may need to extend the range.

CHAIRPERSON PRIOLA: Thank you very much, Dr. Bailey.

We will move on to the open public hearing portion of the afternoon.

DR. FREAS: We have received one request to speak in the open public hearing portion for this remaining Topic 4, and that is Dr. Benjamin Herbage, if you would come to the microphone.

We ask all our speakers in these open public hearings to comment upon any financial affiliations they may have with the issue they wish to comment upon.

DR. HERBAGE: Hi. I would like first to thank the Committee. I am Benjamin Herbage, and I am from the company SYMATESE Biomateriaux. What I would like to present is the European industrial example of BSE risk management policy for implantable collagen of bovine origin.

Next slide, please. As you know bovine collagen is present in many implantable devices,

animal study products, grafts, injectable collagen for aesthetic purpose, tissue -- and other products. SYMATESE Biomateriaux as a collagen manufacturer has been supplying the industry for European medical devices for over 15 years.

Next slide, please. But as you know, when we speak about bovine products, we have to take into consideration the BSE issue, and for European manufacturer it is even more critical, as the disease appeared in the U.K. in the mid-Eighties, and in France at the beginning of the Nineties.

So authorities were prone to issue the guidance and regulation regarding the possibility to transmitting -- of transmitting BSE or TSE agent via medical device. So example of the standards are the following. European standards for use of animal tissue in medical device.

We also have a specific chapter in European Pharmacopoeias, and for the specific case of France you have to submit a file to committee, a French committee, Pharmaco-Biological Safety, to address the risk of transmission of BSE into a patient using a medical device.

Next. So the European approach to BSE management of risk is relying on three different

aspects, and it's starting from the risk analysis, of course, and after that we have two main issues. The first issue is the sourcing conditions, and with the chosen tissue, for example, and control of the animal sourcing; and second main important part is the capacity of production process to inactivate and/or remove prions. To assure that, it's to validate the capacity of the prediction process.

So as a bovine collagen manufacturer, SYMATESE Biomateriaux, always be complied with state of the art risk control.

Next slide, please. So what does that mean for us in terms of sourcing? We have chosen to work with calf hides as long as the hides has never been an infectious tissue, never been -- infectivity has never been detected into hides; and we have chosen to work with animals that are very young, younger than six months old. That has also reduced the risk of the presence of the prions into that kind of animals.

We have a control of crossability. In fact, we have a crossability control of the animals, and we have also specification for feeding. That means we have a specification that a calf needs to be fed with meat diet only, and we, of course, use approved slaughterhouse.

One point that is particularly of importance for us is the control of the slaughtering condition to avoid the possibility of cross-contamination between tissue of different level of infectivity. That means for us the use of killing with intracranial penetration and the removal of the skin before the cutting -- the opening of the carcass.

Before April 2001 we were working with a French sourcing, and we made a move to U.S. sourcing. So we are now working with U.S. hides.

Next. From the side of the process, we, of course, assure the dressability of the product from the hide to the patient, and in our process we include -- we have included the steps that are known to reduce or inactivate or remove BSE/TSE contaminations, and that are mainly different sort of treatments -- on the product we get, three different treatments, sort of treatments, and two treatments are one on dermis and one on the collagen suspension.

We have validated the capacity of the production process to inactivate or remove prions according to European guideline, and it was an animal study. It was using a strain of scrapie, and it has shown that the part of the process investigated had the capacity to remove the infectivity with 5.3 log

reduction. So this was just including one molar sort of treatment and not the first two treatments.

Next slide. So along with WHO control of sourcing and the processing, we have cleaning operation that are intended to clear equipment of the possibility of contamination. That means that we have batch to batch cleaning with an initial cleaning to remove proteins, and then treatment, different kind of treatment, different of the equipment, and followed by rinsing.

Prior to sourcing change we have made the cleaning of all equipment that were in contact with collection, according to the WHO recommendation, and that's what we found. That are the same as the French Minister recommendation for reusable medical device.

That means we choose to use 1 molar sort of treatment on the equipment, and we have also validated the capacity of the cleaning operation to remove proteins.

So in summary, the compliance with the European standards in the use of scientifically based BSE inactivation methods, low restriction -- collection in Europe. So in conclusion, I will maybe ask the Committee to maybe think about promoting the collaboration with other countries like Europe and

other countries in order to maybe increase the collaboration in that field to go to the origin of harmonization in practice for industry.

So I thank you for your attention.

DR. FREAS: Thank you for your comments.

Is there anyone else in the audience who would like to address the Committee at this time? Seeing none, that will end our open public hearing for this meeting.

CHAIRPERSON PRIOLA: We are a little bit behind time, and we all realize that a lot of you have planes to catch, who actually live in places that are accessible from the East Coast on late afternoon flights, where I don't. So I'd like to get to the presentation of the Topic 4 questions. So if we could get those put up, that would be great.

The first part of Topic 4 regards the gathering of ocular tissue from donors that have been discovered to have TSE or possible TSE. And these are -- Some of these are votable questions. Some of the, the FDA is just asking for comments.

So the first question is: Considering all that we have heard, the current practices, the conventional methods of decontamination, the other precautions that are in place, that with regard to

their covering and processing of ocular tissue from donors later discovered to have TSE or possible TSE: Part of this question is does the Committee believe that surgical instruments used in recovery and processing should be destroyed by incineration, if practical? That is in a case of an individual who had TSE or possible TSE.

So it's open to discussion and/or to vote, however the Committee chooses to go. Any comments? Yes, Dr. Wolfe?

DR. WOLFE: Well, based on the now described as nooks and crannies discussion, I think that for the rare instance where this happens there should be no question, it should be destroyed, period. I don't think there is any -- There is no argument against that. It's not going to happen very often, but it's not worth any kind of chance, if it does.

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: I think I agree entirely with Dr. Wolfe. As I understand it, the various instruments are straightforward, inexpensive, easily replaceable. I'm not aware of anything that would cause any difficulty and, given the potential risks, I think the thing to do is destroy them as quickly and as effectively and as completely as possible.

CHAIRPERSON PRIOLA: Dr. Gambetti.

DR. GAMBETTI: Maybe it would be helpful to know what is practical, a definition of practical in this context, or what is practical and what is unpractical?

CHAIRPERSON PRIOLA: I think Dr. Hogan can probably.

DR. HOGAN: Sorry. I think I can shorten this a lot. First of all, how much does one of the sets cost, Ellen?

MS. HECK: About $500.

DR. HOGAN: So these are $500 a set, and I can tell you that the current practice in the eye banks is, if there is any question at all, these are incinerated. So the answer to this question, I don't think -- I think it's moot. Am I correct?

CHAIRPERSON PRIOLA: Well, then we can just go ahead and vote for the record, if there are no objections from the other members of the Committee, because it does seem pretty straightforward.

So let's call for a vote on Question 1-A. Oh, sorry, Dr. Bailar.

DR. BAILAR: Are the words "incineration of" any special significance here? Are we saying that's the way it has to be done?

CHAIRPERSON PRIOLA: Well, that's the way it reads to me, and it's already done. So --

DR. HOGAN: That's the way it is done. It wouldn't be -- There wouldn't be no attempt to decontaminate them.

DR. BAILAR: Would this have the same practical meaning if you took out those two words?

DR. HOGAN: If you took out those words, it would still happen.

DR. BAILAR: Okay.

CHAIRPERSON PRIOLA: Let's go ahead and do the vote. Dr. Solomon? Okay, so the word "incinerate" was in the WHO recommendation.

DR. HOGAN: I would like to just be sure that I'm correct on this point. If I could just ask Dr. Patricia Aiken, am I wrong in any way that these would be, in fact, incinerated?

DR. AIKEN-O'NEAL: I don't know.

DR. HOGAN: This is Patricia Aiken-O'Neal, who is President of the Eye Bank Association of America.

DR. AIKEN-O'NEAL: I don't know that our current medical standards require that. Do they, Ellen? I know that most eye banks do it.

MS. HECK: The current standards don't

speak specifically to it. The problem would be -- and I just want to clarify the problem. It's not a real obstacle. But the way that eye banking instruments are currently processed, it would probably mean an eye bank would destroy all of the instruments in their eye bank, because they would not have been able to track a specific pair of scissors to a specific case.

So we're talking probably about $7-$10,000 worth of instruments that would be destroyed. However, this is if a case is reported to us, and this is not something that has happened in every eye bank would then feel it incumbent to do that, I think, and would generally turn them over according to the recommendations of the institution who handles their disposable waste.

CHAIRPERSON PRIOLA: So because this would be a rare event, impacts on this question in terms of having to dispose of all of those instruments at one time?

MS. HECK: That would be my feeling, because we have not had to do it. We would never take tissue on someone who was a known risk. We simply don't do it, and it would be a reporting of a risk after the fact. The likelihood that the instruments could have been commingled by that chance would be

fairly high, and so all of the instruments would subsequently have to be disposed of unless there is some cycling of how many times it's been disinfected during that process that you felt was adequate.

DR. HOGAN: Let me just say that, if the Committee votes yes on this, I'm sure that the medical standards will be brought to that level.

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: Yes. Somewhere in all the materials that we read, I think we read about some cases of exposure where there were not standards that required destruction of such materials, but the hospitals all opted to destroy them. So I think, you know, this thing is pretty clear.

CHAIRPERSON PRIOLA: Let's go ahead and vote. Bob, do you have a brief comment?

DR. ROHWER: Yes, I do. It's very painful to see instruments thrown away that are a lot better than the ones we use in the lab, and I wish there was an option for people to donate these instruments to TSE laboratories instead of throwing them away.

CHAIRPERSON PRIOLA: Actually, that's a good idea.

DR. HOGAN: Be careful what you wish for.

CHAIRPERSON PRIOLA: Let's go ahead and

call the vote then on this.

DR. FREAS: I'll be going around the table. Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Dr. Bracey?

DR. BRACEY: Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: Yes.

DR. FREAS: Dr. Hogan?

DR. HOGAN: Yes.

DR. FREAS: Dr. Khabbaz?

DR. KHABBAZ: Yes.

DR. FREAS: Dr. Edmiston?

DR. EDMISTON: Yes.

DR. FREAS: Dr. Priola?

CHAIRPERSON PRIOLA: Yes.

DR. FREAS: Ms. Walker?

MS. WALKER: Yes.

DR. FREAS: Mr. Rice?

MR. RICE: Yes.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: Yes.

DR. FREAS: Dr. Stroncek?

DR. STRONCEK: Yes.

DR. FREAS: Dr. Bailar?

DR. BAILAR: Yes.

DR. FREAS: There are 12 voting people at the table. They all voted yes, and I would like to get their comments from the industry rep.

DR. PETTEWAY: Yes.

DR. FREAS: It's unanimous, yes.

CHAIRPERSON PRIOLA: Now Part B of this question is if destruction of instruments is not practical. So I'm not sure we have to address Part B, because we've just said it is practical. If there is no disagreement, we can move on to 1-C.

Okay. Well, 1-C is related to 1-B. Does anybody have any comment on the specific methods listed in the WHO guidelines? All right. I don't see any comment from the Committee, which sort of takes care of 1-D, if I'm reading this correctly, by voting Yes on 1-A.

DR. HOGAN: As I read it, it gets rid of all of question 1.

CHAIRPERSON PRIOLA: Yes, I'm just going down here. Perhaps we should go on to question 1. I think, yes, the other caveats in question 1 all relate to part A, unless there is any objection. Is there any objection by FDA to that? Okay.

All right. So question 2: With regard to

the recovery and processing of ocular tissue, should additional decontamination procedures discussed in question 1 be used routinely; that is, even when TSE has not been suspected?

Comments and discussion from the Committee?

DR. HOGAN: I'll just make a brief comment here. I have been working in this area now for about 20 years, and that is the infectivity specifically of the eye, and I am using this -- looking at the available scientific literature, which we have to this date, I really believe that the cornea is not very infective.

It is infectious, but it's not very infectious. Some of the human data that we have is flawed. There's three cases that we have of transmission. The one from Japan never presented any data at all on the donor, zero. So we don't even know that that donor had Creutzfeldt. All we know is that the index case had a corneal transplant. That's not enough for me.

The data that say that corneas from humans have been transmitted comes from Paul Brown, and there were four transmission attempts involved. Only one of them used cornea only. All the other three patients

had -- it was either whole eye or retina and lens or cornea and lens, which -- The lens is more infectious than the cornea.

So there's about 105 logs of infectivity based on incubation period titers to the cornea as opposed to 108 in the retina. So the cornea is not as bad.

Now the procedures that are used in the eye bank, even if a whole eye is a nuclei, not just the front of the eye, you never go behind the lens. You are always in front of the lens when you harvest a cornea. So the more infectious portions of the eye are not entered.

So you have a potentially infectious piece of tissue there, but it would be at the low end of things. So first of all, you are screening. So you are getting rid of a lot of patients that might have potential. You are already using barrier techniques. You are already using aseptic techniques.

In my sense, I don't think adding routinely two hours or one hour of sodium hydroxide to the benches when you're already using barrier drapes is going to add much. It is going to significantly slow down the acquisition of material.

On one weekend some eye banks can have

four or five corneas that they are trying to do, and it would mean a lot of time, a lot of labor, in between these cases. That's my take.

CHAIRPERSON PRIOLA: Dr. Khabbaz?

DR. KHABBAZ: Yes. If I understood correctly, what's being done is perhaps, even though least effective, is one procedure that follows under the WHO recommended decontamination methods, meaning 134 degrees Centigrade at 18 minutes. So it is a recommended procedure by experts.

The one thing that I would recommend, though, if I heard correctly, is to try to tighten the screening procedure. There was some discussion of some states allowing actually inclusion of patients that should be excluded, based on history.

CHAIRPERSON PRIOLA: Yes, history should be taken at least. Oh, Dr. Solomon?

DR. SOLOMON: What they are doing currently, the 134C for 18 minutes is the least effective of the six -- The method that is currently being used, the 134C for 18 minutes is the least effective of the six methods used, and that is why one of the questions in subparts of question 1 asked would a procedure that involved sodium hydroxide or sodium hypochlorite -- would that be necessary to have an

adequate procedure?

CHAIRPERSON PRIOLA: Well, if I recall, I made some notes when Ms. Heck was talking, and there were multiple steps to the procedures used, at least to sterilize these instruments, including keeping them moist, steam autoclaving, recleaning, disinfecting, right packaging, reautoclaving.

All of those autoclavings -- are they at 134 degrees for 18 minutes or is it just the final one? I was a little confused there.

MS. HECK: There's some variation, I think, among banks currently. The first autoclaving is at 134 for -- I think we do use 18 minutes, and the last one is at 121 for 30 minutes.

CHAIRPERSON PRIOLA: And that first one is on moist instruments?

MS. HECK: Yes. The first one is done usually in a pan with a small amount of water still remaining on the instruments in the pan during the sterilization.

CHAIRPERSON PRIOLA: So I would think that's pretty extensive and even close to the WHO recommendations, even if it's one of the less effective ones.

MS. HECK; The disinfections that are used

are commonly used in sterilizing instruments in the OR like Cydex and all those other subsequent treatments.

CHAIRPERSON PRIOLA: Other comments? Dr. Edmiston?

DR. EDMISTON: I have to add my support to these comments. Actually, I was not aware of how complete the process is in the eye banks. I have to give you a gold star from the infection control perspective, and I really think you are above and beyond the call in terms of screening the patients, and then the evidence has been projected about actually barriering the infectivity by virtue of the fact you're not entering the eye proper. I'd have to support the procedures in place.

CHAIRPERSON PRIOLA: Other comments or discussion? Should we call for a vote then on question 2? So with regard to the processing and recovery of ocular tissue, should additional decontamination procedures be used routinely even when TSE has not been suspected?

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Dr. Bracey?

DR. BRACEY: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.
DR. FREAS: Dr. Hogan?
DR. HOGAN: No.
DR. FREAS: Dr. Khabbaz?
DR. KHABBAZ: No.
DR. FREAS: Dr. Edmiston?
DR. EDMISTON: No.
DR. FREAS: Dr. Priola?
CHAIRPERSON PRIOLA: No.
DR. FREAS: Ms. Walker?
MS. WALKER: No.
DR. FREAS: Mr. Rice?
MR. RICE: No.
DR. FREAS: Dr. Wolfe?
DR. WOLFE: No.
DR. FREAS: Dr. Stroncek?
DR. STRONCEK: No.
DR. FREAS: Dr. Bailar?
DR. BAILAR: No.
DR. FREAS: There were 12 voting people who just voted. And now our industry comments?
DR. PETTEWAY: No.
DR. FREAS: Unanimous, no.
CHAIRPERSON PRIOLA: I guess we can go on to question 3, which is a variation of the previous

two questions. That is: Should similar decontamination procedures be used for instruments and surfaces used to recover and process other tissues with a low risk of TSE infectivity that are derived from cases of a known or suspected TSE?

So this has to do with low risk tissues from a patient with or suspected of having TSE. So this gets, I think, in part to what Dr. Hogan was approaching. Is that right? With the removal of the cornea versus the lens versus --

DR. HOGAN: Right. I'm not sure that this question means other ocular tissue, because there is no other ocular tissues that are utilized. I assume you mean other like kidneys or something else like that. But I'm not sure we regulate that.

DR. SOLOMON: That's correct. I meant musculoskeletal tissue, skin, those other types of tissues other than ocular tissue.

DR. HOGAN: And my sense is we've already talked about a relatively high risk tissue, as far as we know, compared to those others. But most hospitals are going to incinerate those instruments, pretty much regardless of how much they cost, in musculoskeletal.

So we haven't talked yet about other decontamination procedures other than incineration.

Maybe you want to bring that up.

CHAIRPERSON PRIOLA: So I want to make sure I understand then. This question doesn't refer specifically to ocular tissue. This is now a very general, every other tissue in the -- low risk tissue in a person? Okay. Sorry, Dr. Bailar?

DR. BAILAR: And I assume this applies when the suspicion of TSE arises after the tissues have been harvested?

CHAIRPERSON PRIOLA: I'm sorry.

DR. BAILAR: I assume that this question applies when the suspicion of TSE applies -- comes up after the tissues have been harvested? What do you go back and do?

CHAIRPERSON PRIOLA: Dr. Khabbaz?

DR. KHABBAZ: It would have to be, because you wouldn't -- tissues from patients with TSE.

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: Yeah, these are low risk tissues, but I guess the question that comes to my mind is I really don't know the practices of those other banks. We've had a fairly elaborate discussion of what the eye banks do, but not really what the tissue banks do, the other tissue banks.

DR. HOGAN: Well, skin is considered a low

risk tissue, and Dr. Heck also works in skin harvesting. Maybe she can help us with that.

CHAIRPERSON PRIOLA: Yes, Ms. Heck?

MS. HECK: Thank you. I also -- Our facility is a skin and bone bank, and we have not customarily sterilized instruments by the higher temperatures. I have to make you aware that the dermatome, for instance, could not withstand that. It's an instrument that would not withstand some of the treatments that are proposed with sodium hydroxide or hypochlorite, or the higher level of sterilization.

Now we do go through the decontamination of cleaning regimes and removing gross contamination, and then sterilizing. But at the present time, to the best of my knowledge, no one is doing the same rigorous sterilization that we are performing with the eye banking instruments on osteotomes or dermatomes.

DR. HOGAN: So can I take that comment to mean that, if you had a case of Cruetzfeldt that you had used a dermatome on, that you couldn't decontaminate it. So you would have to incinerate it?

MS. HECK: I think that that would be a -- Yes, that would be a consideration, Dr. Hogan. The parts of the dermatome which came in contact with the patient, meaning those parts other than the motor,

would probably have to be incinerated.

Again, this has not been a situation which we have faced, I'm giving you an opinion based on what I think would happen, not what we have any data to support, because we haven't faced it, but we do do similar screening for tissue retrieval in bone and skin.

CHAIRPERSON PRIOLA: Dr. Edmiston?

DR. EDMISTON: Keep in mind, we had a discussion similar to this yesterday regarding high risk patients with low risk tissues and that the option -- There is an option or a number of options, but one of the options in the CDC guideline is that those instruments can be reprocessed within the hospital, and quite often that does occur.

CHAIRPERSON PRIOLA: And that's based on the low risk -- the low infectivity in the tissue.

DR. EDMISTON: Right.

CHAIRPERSON PRIOLA: Yes, Dr. Schoneburg?

DR. SCHONEBURG: I think it might be useful to review what a low risk tissue is. I've always regarded skin as basically a no risk tissue. You have a list, I know.

CHAIRPERSON PRIOLA: I've got the list -- or Dr. Solomon?

DR. SOLOMON: I was very loose with the word low. What I meant by low is anything that's not high. So that would include medium, low and no detectable.

CHAIRPERSON PRIOLA: And this list of tissues is -- Dr. Gambetti?

DR. GAMBETTI: I think here we have to keep in mind that we are dealing with a moving target, because tissues that were like the skeletal muscle or even the spleen in sporadic CJD that were considered to be essentially clear of prions, now with a better method of detection with more frequent full autopsies and, therefore, analysis of these tissues in more cases of sporadic CJD, prions are detected also in these tissues occasionally.

We know also that the spleen is now a target organ even in experimental scrapie after intracerebral injection. So we are dealing with a moving target. These tissues are -- The probability that prions, infections prions, exist in these tissues are increasing, and already have increased.

In our practice, we consider really all tissues that come from a case of CJD infectious.

CHAIRPERSON PRIOLA: Other comments? Yes, Ms. Heck?

MS. HECK: Based on his moving target and because I do other things, a question occurs to me, that by and large, as we've looked at femur removal or skin removal, we've not thought about this as having a high level of risk. But more and more, we are being asked to remove vertebra, and I wonder if the removal of vertebra would constitute a different level of risk and, if in that case, the instruments which, for the most part, I see no problem with sterilizing at higher temperatures -- and these are quite hardy instruments, osteotomes and hammers -- might be in a different category if they were used for vertebra?

CHAIRPERSON PRIOLA: Dr. Gambetti, do you have a response to that?

DR. GAMBETTI: I don't claim that, for example, in these condition, tissue -- instruments have to be destroyed, but certainly I am emphasizing the need to do thorough decontamination.

So I could consider the two possibilities, that in one case tissue are destroyed by an incineration, and in the other be simply gone through a process of decontamination and sterilization.

CHAIRPERSON PRIOLA: And that is because, even though this is your moving target, it's still a low risk tissue in terms of the level of infectivity?

Well, if an extra decontamination procedure should be used, should it follow the WHO guidelines or are there suggestions as to how that could be done? That was sort of the gist of the B-C-D-E of question 1, which now comes back to haunt us, I think, in question 3.

So are there any comments on that from the Committee?

DR. EDMISTON: Well, let me get this straight. Let's just sort of enumerate the tissues now. We're talking about skin. We've discussed eye. We're talking about skin, talking about bone. Other tissues are going to be harvested from the site, in most cases, where the patient has died by usually from -- quite often by a member of the surgical staff. They may be flying down there -- Are we talking about solid organs? Are we talking about solid organs? No, we're not? Are we?

CHAIRPERSON PRIOLA: Dr. Solomon?

DR. SOLOMON: The only reason not to talk about them is FDA doe snot have jurisdiction over them. HRSA does.

DR. EDMISTON: So we're talking about primarily bone and skin. Did I miss anything else?

DR. GAMBETTI: Well, I heard the name skeletal muscle. I heard the word. I don't know whether we are talking about skeletal muscle and internal -- other internal organs like spleen, liver, lung.

DR. EDMISTON: I think we need to clarify what tissues we are talking about, especially because there are certain tissues that do not fall within your jurisdiction.

DR. SOLOMON: They would be bone, tendon, ligament, skin, ocular including cornea and sclera, and also veins, arteries, veins, vascular tissue. It would include that.

CHAIRPERSON PRIOLA: So that would all be considered low risk tissue with the qualification of the moving target.

DR. GAMBETTI: There is a recent publication in which the presence of -- at least by -- no, also I think by Western blot of scrapie prion protein in the vessel wall has been shown. So that would be -- Again, a situation again one target that was moving now has been found.

CHAIRPERSON PRIOLA: So once again then, I guess, it gets back to decontamination, that if the Committee considers this an issue that requires extra

decontamination, should it be done according to the guidelines that have already been laid out by the WHO or do we have something else to recommend? Any comments?

DR. HOGAN; I would just suggest that it's one of the higher levels of decontamination using -- if they can't incinerate -- sodium hydroxide plus sterilization. You can't use hypochlorite on these instruments. So hydroxide plus sterilization in some combination, either in hydroxide -- Essentially, number one or two, I think it is, on the WHO guidelines. That would be my suggestion.

DR. GAMBETTI: Claving also.

DR. HOGAN: That's what I mean, hydroxide plus autoclaving.

DR. GAMBETTI: In other words, the full process like for a surgical instrument?

CHAIRPERSON PRIOLA: And would that be something that could be done, if it had to be done, in the case of -- This is always, of course, in the case of known or suspected TSE. Is it something that could be done in one of these facilities? Ms. Heck, can you speak to that, just in those cases, I guess, of suspected or confirmed TSE?

MS. HECK: Again, in all likelihood, the

instruments would have been commingled, and all of the instruments would need to be taken through this process. But I believe that they could be, except for the dermatome, as I mentioned earlier.

CHAIRPERSON PRIOLA: Does the Committee feel comfortable voting on this?

DR. FERGUSON: Can you clarify exactly what we are voting on?

CHAIRPERSON PRIOLA: Okay, I was afraid you were going to ask that. Well, I think, if anyone has a different opinion, please speak up. The thing that holds me up is similar decontamination procedures, because we haven't talked about them before, which is why I keep bringing up the WHO guidelines and, you know, what Dr. Hogan just said addresses that.

So I suppose we should decide that, if we vote yes for that, we need to know what decontamination procedures we want to recommend. Any comments? Are the WHO recommendations sufficient, in the opinion of the members of the Committee?

DR. EDMISTON: I think they make a good baseline. The reason why I say that is that, in terms of native vessels, if you have a vascular or transplant service, we routinely do remove vessels and

store them. You may need them in patients who are developing vascular access, need a little bit of vessel to make that connection.

Those, as a rule, are stored one to two weeks. I think it would be -- The question always comes up in the operating room, what are the risks associated with that. So I think, as a baseline, that would be a good recommendation.

CHAIRPERSON PRIOLA: So should we vote on the question and make it clear that, by similar decontamination procedure, we mean that to follow the WHO guideline, should this situation occur under these circumstances? Is that agreeable? Okay.

So then let's vote on question 3, which is: Should similar decontamination procedures -- and that is understood to be the WHO guidelines for dealing with low risk TSE tissues -- be used for instruments and surfaces used to recover and process these tissues from cases of known or suspected TSE?

I'm sorry. Dr. Solomon?

DR. SOLOMON: So again, you would vote for all six as a group or would you differentiate, as Dr. Hogan has, those that include sodium hydroxide versus the number 6 that does not?

CHAIRPERSON PRIOLA: Well, that's why I

put in the low risk. Whatever they require for low risk tissue, and what is their specific requirement for low risk tissue, or do they have one? Is it just the choice of the facility?

DR. EDMISTON: You better put those six up again, because now I'm unclear. All right? Could you actually enumerate all those for me, just without putting it up?

DR. ASHER: As I pointed out yesterday, the first four guidelines include either sodium hypochlorite or sodium hydroxide at elevated temperatures. Now we have already seen evidence and heard why sodium hypochlorite is not suitable for reprocessing metal instruments, which really leaves sodium hydroxide.

The question is whether a method incorporating sodium hydroxide is indicated; if so, at an elevated temperature? Not having heard any objection to elevated temperatures with this kind of instrument, that reduces the choice, it appears to me, to choosing between the WHO recommended method like Method 1 -- and you should have a list of them, which Ruth can read again or flash up again, if you want -- or Method 6, which is 134 for 18 minutes.

But recall that Method 6 comes with the

disclaimer that, if tissue has been baked on, then some residual infectivity will remain, and we can't ignore that part of the WHO guideline either. One would hope that most of the time that wouldn't happen, but it was a proviso, a concern expressed by the WHO consultation as being a potential problem at the time of the publication of the document.

CHAIRPERSON PRIOLA: Okay, Dr. Hogan?

DR. HOGAN: I'm sorry to prolong this. But I think heated hydroxide is going to be a little bit of an issue perhaps to safety. How about just hydroxide in some combination with autoclaving, according to the WHO guidelines. Take out hypochlorite, which gives you the first four, I believe -- first five? -- but not the sixth.

CHAIRPERSON PRIOLA: I'm sorry. Lisa?

DR. FERGUSON: This may be a somewhat silly question. I guess, for purposes of this Committee, I understand the fact that the sodium hypochlorite is harsh on the instruments, but as I understand it, this Committee is being asked essentially to comment on the science of it, and do we think those processes are adequate to disinfect the instruments.

Do we need to get that specific to say,

yes, this one but not this one, because it's harsh on the instruments or should we just focus on do we think any of those would be adequate, and leave it up to the individual facilities, whatever, to decide whether their instruments can stand it or not?

CHAIRPERSON PRIOLA: I was trying to think of all the data we were presented yesterday by Dr. Rohwer and Dr. Taylor. That wet autoclaving at 134 degrees for a significant period of time is actually pretty effective. It can inactivate several logs of infectivity, if I'm recalling right.

So even the low risk tissue -- Given this is a low risk tissue, even that might be sufficient under these circumstances. So perhaps you're right. Maybe it's okay to leave it up to the individual facility, if it follows one of those six guidelines, although that introduces variability.

Bob, do you want to make a comment?

DR. SOLO: Could I make a comment?

CHAIRPERSON PRIOLA: Oh, I'm sorry. Sure.

DR. SOLO: I'm Dr. Yolanda Solo. I am an orthopedic surgeon. I am also a medical director for a tissue bank. There's just like a couple of quick comments.

First off, I disagree with regard to the

vertebral bodies. I think, if you are harvesting those, you are awful near to at risk tissue to throw that into the same pot with other bone, and also to throw out into that, when you are talking about bone and you are talking about skeletal muscle, they have got to go through an awful lot of skeletal muscle to get to the bone to harvest, just for what that's worth.

If the Committee really thinks that these things that WHO has described are going to be effective for sterilization, then in my mind they would apply to all of it. If there is any question, I can only tell you that in the tissue bank industry we have enough troubles right now. The last thing that I think we need is to say that this would be a proper thing and not to throw these instruments out, and then have a problem with this.

I don't know how often, and maybe Ellen can actually give me how often it's even come to mind after the fact that someone who has been a tissue donor has then been suspected of having a TSE, because that's a criteria for elimination.

I would recommend at this point, while we don't know what any of these things are really going to be effective in sterilizing those instruments, that

throwing them out is a little bit safer at this point in time. And as an orthopedic surgeon who implanted bone, it's a worry for me to say that we could do this and in the meantime you could contaminate a whole bank and continue to do it, just because you don't want to throw those instruments out.

CHAIRPERSON PRIOLA: Thank you. Dr. Rohwer, do you want to make a comment?

DR. ROHWER: I just want to point out that these WHO guidelines were ranked in this order to accommodate worldwide needs, not just Western medicine, and the idea -- Some of these things at the bottom of the list are there, because there are places that could not accommodate -- We are trying to accommodate people who don't have electricity. Okay? They can still boil things in sodium hydroxide.

So I think you have to be careful about endorsing the entire list. That was not the intent of the list, in the first place.

CHAIRPERSON PRIOLA: Thank you. That's good to know, actually. Any other comments from the Committee? Dr. Gambetti?

DR. GAMBETTI: Is there a way to have an idea of how often a tissue bank will face a situation as the one indicated in question number 3 for so

called low risk tissues? In other words, how often one would expect -- Of course, the idea to see how much would be the cost of actually destroying the instrument in such instance?

CHAIRPERSON PRIOLA: Ms. Heck, can you address that?

MS. HECK: I don't know that there is any information available on how often that would occur. I would venture to say that it is very, very rare, because in all of the meetings I have gone to in the American Association of Tissue Banks in the last 20 years, I have not heard of a case.

So I think the incident where they would have to throw out all of their instruments is rare. I can tell you that we did encounter one case this year where, had we been the individuals taking the tissue, on subsequently reviewing a case from someone else, we would have recommended that the tissue not be taken from that, and that would have constituted one out of the thousands of cases that were done this year that that would apply to.

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: Yes. I was thinking about this before, but it just actually hammered me a little bit. That is the issue of commingling. It would seem

that, if there is a theoretical risk, that it would be best to keep the instruments together as a packet, because then -- In other words, you would not increase the risk for exposure. It would seem to me to be best tissue practice.

CHAIRPERSON PRIOLA: I guess my last thought is, still getting hung up on this similar decontamination procedure issue, if it is a rare event, could we recommend that -- Since we voted before that incineration is the way to go for a group of contaminated instruments, could we put that in? That's what we recommended for decontamination in question 1. Could we put this here, too, that they should be incinerated as well, given that it seems to be a low risk tissue, a low priority event, and perhaps a cost that would be incurred only once every -- once every what? Yes, 120 years or so.

Would that be one way to get around this phrase? What would FDA --

DR. SOLOMON: I just want to point out some of the instruments we are talking about are large saws. They are huge. These are the equipment that are probably quite expensive. They are not just scalpels and scissors.

CHAIRPERSON PRIOLA: Lisa?

DR. FERGUSON: I guess -- I mean, I could see -- I can see the logic in that for such things as vertebral column. I don't see the logic or the science in that for skin or, you know, tendons, ligaments.

CHAIRPERSON PRIOLA: Should we vote on this? Is there further discussion? Does anyone want to recommend a modification to make it easier for them to vote or do we all feel we can vote on it? Dr. Ferguson?

DR. FERGUSON: I would suggest a modification. Perhaps we could pull out, you know, bone or specifically vertebral column and make that a separate category.

CHAIRPERSON PRIOLA: You mean from the list of low risk TSE tissues?

DR. FERGUSON: Yes. We would be saying --

CHAIRPERSON PRIOLA: What Dr. Asher just said, it's a high risk material, the vertebral column, because of the spinal cord.

DR. FERGUSON: Okay. So we are not even including vertebral column in here? Okay. Okay. Never mind.

CHAIRPERSON PRIOLA: Go ahead then. If no one else has any further comments, can we vote on

this? Okay. Go ahead and call the roll.

DR. GAMBETTI: Change the order again.

DR. FREAS: I will attempt to reverse the order, starting with you, Dr. Bailar.

DR. BAILAR: Yes.

DR. FREAS: Dr. Stroncek.

DR. STRONCEK: No.

DR. WOLFE: Could we just clarify, because we've got a change, and it wasn't changed in the question. So are we saying destroy all instruments in association with a case that turns out to be CJD? Is that it? It's a modification of 3, I suppose. Right?

CHAIRPERSON PRIOLA: Comment from the Committee? Do we mean destroy or just follow WHO guidelines, because those were the two things we were discussing. Is that right?

DR. WOLFE: Which is it?

CHAIRPERSON PRIOLA: Right. So which is it?

DR. WOLFE: Which portion needs to be made clear? That's all.

DR. EDMISTON: I was under the impression it was following WHO guidelines. Correct?

CHAIRPERSON PRIOLA: That would be my choice, to follow the WHO guidelines.

DR. GAMBETTI: Yes means what?

CHAIRPERSON PRIOLA: Yes would mean should similar decontamination procedures -- that is, following the WHO guidelines -- be used for instruments with the low risk tissues?

DR. GAMBETTI: And no implies the incinerate -- implies incineration?

CHAIRPERSON PRIOLA: I would think so. Well, I don't know if I want to say that. I don't know what no would imply. Dr. Epstein?

DR. EPSTEIN: Yes. I think it would be clarifying here if the Committee first voted the question with a recommendation to incinerate where possible, and then if the Committee does not favor that option, then to vote the question follow WHO guidelines, because then the FDA gets more advice. And you can actually vote both questions and just see where you are.

DR. WOLFE: What does "where possible" mean, though? Who can decide what's possible?

DR. EPSTEIN: You know, we are dealing in a domain of guidance here, and we are trying to figure out just what do we really think? I mean, if what you really think is that the ideal answer is destroy the instruments, then that's what we need to hear.

Now there may be situations where that is not possible, and we would have to address them, and there will be clarifications, you know, caveats, exceptions, work-arounds, etcetera. But what we are looking for is the scientific advice of the Committee.

If the scientific advice is destroy, then we ought to get a clear message. We are not going to get it if we only vote the question with WHO recommendations, because they span the gamut.

So I think it's best to vote the question twice. First, let's see what the Committee thinks about a recommendation to incinerate -- equal destroy -- and then let's see what the Committee thinks otherwise.

DR. EDMISTON: Now we are talking about low risk tissues. Correct?

DR. EPSTEIN: We are talking about low risk tissues in the case of known or suspected TSE in the donor.

DR. EDMISTON: And the vertebral column is excluded? That's a high risk tissue.

DR. EPSTEIN: I think it's been clarified that we would regard that as high risk tissue.

DR. EDMISTON: All right.

CHAIRPERSON PRIOLA: Okay. So then the

question should be rewritten, basically along the lines of question 1-A, that: Should instruments used to recover low risk tissues from TSE patients be incinerated, if they come from the case of known or suspected TSE?

So then voting on this would be Yes or No for destruction of these instruments.

DR. FREAS: Okay. Again, I'll start with Dr. Bailar.

DR. BAILAR: I say they should be destroyed. I thought that's what I was voting for last time.

DR. FREAS: Dr. Stroncek.

DR. STRONCEK: Yes.

DR. WOLFE: Yes.

DR. FREAS: Dr. Wolfe with a Yes. Mr. Rice?

MR. RICE: Yes.

DR. FREAS: Ms. Walker?

MS. WALKER: Yes.

DR. FREAS: Dr. Priola?

CHAIRPERSON PRIOLA: Yes.

DR. FREAS: Dr. Edmiston?

DR. EDMISTON: I am going to say No.

DR. FREAS: Dr. Khabbaz?

DR. KHABBAZ: Abstain.

DR. FREAS: One Abstain. Okay. Dr. Hogan?

DR. HOGAN: Yes, where practicable.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: I guess I would have to agree, Yes where practicable. That's my hang-up.

DR. FREAS: Dr. Bracey?

DR. BRACEY: No.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Okay. There was one abstention, two No votes, hopefully nine Yes votes.

CHAIRPERSON PRIOLA: Would it be possible to insert that phrase "where practical" to accommodate? You're right. It's already there. We can vote now on the second version of this, if the Committee would like, although I am rather assuming the second version would be the inverse of what we just voted on, which is that: Should the WHO guidelines be used for decontamination of instruments and surfaces used to recover tissues from low infectivity?

Jay had asked if we would vote on both. Does the Committee feel that's necessary, having voted

on this first one? I don't think that it is, really, either. I think it's clear, yes, what the Committee is getting at.

Okay. So if there are no objections from the Committee or anyone else, let's move on to the final question, Question 4, which is: With regard to recovery and processing of other tissues with a low risk of TSE infectivity, should additional decontamination procedures be used routinely, even when TSE has not been suspected?

Any comments or discussion from the Committee on this? Dr. Wolfe?

DR. WOLFE: Well, even though this is being asked in the ocular context, the question as stated means does anytime anyone is operated on for anything, should you have routine decontamination, because we've left the eye presumably. So the question can't be separated from any other kind of surgery.

So the question really is anytime anyone is operated on, even though there is no suspicion of TSE, should these extra decontamination things be used? I think that's what the question is.

CHAIRPERSON PRIOLA: Dr. Solomon, did you want to say something there?

DR. SOLOMON: Well, in my mind, since on question there was a unanimous No vote for ocular tissue, which is a high risk, I'm thinking with a low risk it would also be a unanimous No.

CHAIRPERSON PRIOLA: I'm pretty sure that's -- Yes. I completely -- I'm pretty sure that's the way it is going to go, but I wanted to make sure everybody was -- Is everyone comfortable with voting on this one? Okay. So let's call for the vote on Question number 4.

DR. FREAS: In reverse order, Dr. Bailar?

DR. BAILAR: No.

DR. FREAS: Dr. Stroncek?

DR. STRONCEK: No.

DR. FREAS: Dr. Wolfe?

DR. WOLFE: No.

DR. FREAS: Mr. Rice?

MR. RICE: No.

DR. FREAS: Ms. Walker?

MS. WALKER: No.

DR. FREAS: Dr. Priola?

CHAIRPERSON PRIOLA: No.

DR. FREAS: Dr. Edmiston?

DR. EDMISTON: No.

DR. FREAS: Dr. Khabbaz?

DR. KHABBAZ: No.

DR. FREAS: Dr. Hogan?

DR. HOGAN: No.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: Dr. Bracey?

DR. BRACEY: No.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Unanimous, No.

CHAIRPERSON PRIOLA: Well, that's good. We are consistent.

So let's go on to the questions now for Part 2 of Topic 4, which now switches from the question of higher risk ocular tissue to low risk plasma derivatives and the possibility of essentially cross-contamination of equipment with plasma from potential vCJD individuals.

So the question is: Considering current facility cleaning practices, the low risk of variant-CJD infectivity in human plasma, and the ability of plasma fractionation methods to clear TSE agents:

Does the Committee feel that current facility cleaning methods -- that is, the use of solutions of sodium hydroxide or sodium hypochlorite

followed by extensive rinsing cycles -- are adequate to minimize the possibility that an infectious dose of vCJD agent may be carried over from one manufactured lot to the other?

So I think "minimize the possibility" is the key qualifier there. Any comment and discussion from the Committee? Yes, Dr. Petteway?

DR. PETTEWAY: Yes, just one qualifier here. That is that you have to be careful. These are complicated processes, and there are tubes and gaskets that run from one pot to another, one vessel to another. They are there to minimize the risk of cross-contamination, cross-contamination of product, for efficacy and safety, and then cross-contamination relative to viruses or bacteria.

This is not to say that you may not be able to increase the stringency of cleaning that exists today, but you have to be extremely careful, because if you do it, you may degrade already existing safety parameters that are in place, that are in place for another reason.

I think that's an important consideration.

CHAIRPERSON PRIOLA: Other comments? Oh, I'm sorry, Dr. Scott.

DR. SCOTT: Yes. I think I just want to

point out a couple of things. One is we have asked you about current facility cleaning methods and, obviously, we haven't presented all of those. But what you did see in the PPTA presentations, I think, was a moderately wide range of what can be done.

So you have solutions as low as 0.01 molar sodium hydroxide being used in some cases, and as high as at least 1.0 molar. So there is a broad range, and I think that, if you say Yes or No or Maybe to this question, that's okay; because the most important question, I think, to us is question 2. That is, whether or not, on a scientific basis, we should start to consider perhaps looking at at least minimum types of standards or recommendations for a minimum.

DR. EDMISTON: My recent memory seems to tell me that we actually had data presented to us that suggests, strongly suggests, that 0.1 molar -- is that correct? -- 0.1 molar was appropriate concentration for inactivation of these entities.

So I think we are getting -- We almost have the answer to 2 right there, based on that.

CHAIRPERSON PRIOLA: Particularly, given the low risk nature of the material. Shall we vote on question 1, which is simply: Do we feel that the current cleaning methods are adequate to minimize the

possibility of transfer of an infectious dose of the vCJD agent from one manufactured lot into the next? And that is plasma derivatives, low risk -- extremely low risk tissue.

DR. WOLFE: It should be just CJD, not just vCJD. Right? It's all CJD.

CHAIRPERSON PRIOLA: Well, I think the issue here is cross-contamination with European plasma, and that concern is vCJD.

DR. WOLFE: But the current methods were not intended for that, since there hasn't been -- That's what the question is. Should the current methods that are being used for other things -- are they good enough to also take care of the vCJD? That's what the question is. Right?

CHAIRPERSON PRIOLA: Right. Yes? Do we feel comfortable voting Yes/No with no alteration in the question or changes? Okay, let's go ahead and do that then.

DR. FREAS: Okay, this time I will go back to Dr. Gambetti.

DR. GAMBETTI: Yes.

DR. FREAS: Dr. Bracey?

DR. BRACEY: Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: Yes.
DR. FREAS: Dr. Hogan?
DR. HOGAN: Yes.
DR. FREAS: Dr. Khabbaz?
DR. KHABBAZ: Yes.
DR. FREAS: Dr. Edmiston?
DR. EDMISTON: Yes.
DR. FREAS: Dr. Priola?
CHAIRPERSON PRIOLA: Yes.
DR. FREAS: Ms. Walker?
MS. WALKER: Yes.
DR. FREAS: Mr. Rice?
MR. RICE: Yes.
DR. FREAS: Dr. Wolfe?
DR. WOLFE: Yes.
DR. FREAS: Dr. Stroncek?
DR. STRONCEK: Yes.
DR. FREAS: Dr. Bailar?
DR. BAILAR: Yes.
DR. FREAS: And the industry position?
DR. PETTEWAY: Yes.
DR. FREAS: That's a unanimous Yes.
CHAIRPERSON PRIOLA: So we move on to the second question, and that is: Are the available scientific data sufficient for FDA to recommend

specific methods for cleaning of equipment used in the manufacture of plasma derivatives with respect to TSE agent clearance or inactivation?

So this is for recommending specific methods for cleaning.

If so, please identify which methods can be recommended. If not, please describe what additional studies would assist in development of such recommendations.

So we have just voted that the current cleaning methods are adequate. Dr. Bracey?

DR. BRACEY: I guess my perspective would be one of hesitance, knowing that it sounds as though there are good studies that are being planned, and to in essence set a standard now might be premature.

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: I agree. I think things are developing rapidly enough that I would not want to lock FDA and the industry into using something when something better may come along pretty soon.

CHAIRPERSON PRIOLA: Dr. Hogan?

DR. HOGAN: Plus, as I think we've talked about in these other circumstances, recommending something specific has been tough for us, and especially taken in regard to complexities of the

machinery and the design -- and safety designs are built in.

I don't know how we could do that, but then I've said that before.

CHAIRPERSON PRIOLA: Yes, Dr. Stroncek?

DR. STRONCEK: On the other hand, they are not asking us to give their recommendation. They are just asking for advice if they should, and the problem will be that we think industry is doing now is fine, but there is nothing to say a new company coming along would have to abide by those rules that the current manufacturers use.

CHAIRPERSON PRIOLA: I'm sorry. Dr. Petteway.

DR. PETTEWAY: Yes. I assume that this means over and above what is currently done, in addition to what is currently done.

CHAIRPERSON PRIOLA: Is that right, from the FDA? This means over and above what is currently done, which we just voted as adequate?

DR. SCOTT: Well, as we are discussing, some of the methods now might certainly be considered adequate. In fact, I think the Committee thinks, based on the information that we've seen, that it is quite likely that many of them are.

I think it's more a question of establishing a minimum across the board. At least in my mind, it is whether or not we are at a point where we could or would want to do that.

CHAIRPERSON PRIOLA: So by voting that the current conditions are adequate, does that imply that we meant that's the minimum that should be done? Dr. Bailar?

DR. BAILAR: I don't read this as unidirectional that way. The first question had to do with whether what they now do is adequate. The second has to do with instructing the industry on how to do it.

CHAIRPERSON PRIOLA: Which could be to keep doing what they are doing, in one sense.

DR. BAILAR: It could be to go on with what you are doing. On the other hand, something else may come along that would not be added but would replace what is now being done. I wouldn't want to preclude that possibility.

CHAIRPERSON PRIOLA: Please go ahead, Dr. Wolfe.

DR. WOLFE: My only question is how standardized is it within the industry as to what is going on, because maybe FDA's question is, if nine out

of ten or 99 out of 100 are doing one thing, and one isn't, do they have the authority to at least impose a normative standard for what most people are doing now, wait for the results of the subsequent -- the studies that are going on, then notch it up some.

CHAIRPERSON PRIOLA: Actually, I think that's a really good point, and it seems from what Dr. Scott had just mentioned that there is some variation in the way that this is done. So I think that's an excellent point, in which case we are saying that -- we would be saying that right now it's adequate. What they are doing is fine, but we would -- Would we like more specific experiments geared toward --

DR. WOLFE: Well, I'm just saying that what is being done now should be standardized, so that everyone has to do whatever the FDA decides the normative of what is being done now is, and then add more based on new studies.

CHAIRPERSON PRIOLA: With or without new data?

DR. WOLFE: With new data. I mean, pending the studies that we heard described.

CHAIRPERSON PRIOLA: Dr. Weissmann, do you want to make a comment?

DR. WEISSMANN: Regarding the

standardization, I would like to point out, people have been talking all the time about using 1.0 molar sodium hydroxide. However, one has to specify that the pH of the solution at the end of the procedure must be the same as in the beginning, and the amount of tissue which is being exposed to sodium hydroxide has a big influence on that, because if you take a lot of tissue and little sodium hydroxide, your pH is going to drop to almost neutral. So it's not going to have the effect which is required.

So I think the essential point is to control the pH at the end of the process, and make sure that it still corresponds to 1.0 molar sodium hydroxide.

DR. WOLFE: And that's an example of standardization, I think, too.

CHAIRPERSON PRIOLA: He said that's an example of standardization of the process. Right.

DR. WEISSMANN: I think it is very important, because to begin with, you take a 1.0 molar solution of sodium hydroxide which has been standing around for a day, and it really isn't 1.0 molar anymore, because it picks up all the CO2 from the atmosphere.

So I mean, it's not enough to say 1.0

molar sodium hydroxide.

CHAIRPERSON PRIOLA: Dr. Petteway?

DR. PETTEWAY: Actually, that's a very good point, and it is taken into account in the current cleaning protocols and procedures, especially the amount of tissue per se relative to contact with sodium hydroxide in the concentration and the preparation and the use of sodium hydroxide in a temporal manner. That's taken into account in these cleaning protocols.

DR. WOLFE: And are all companies doing that? That's my question.

DR. PETTEWAY: But they are doing it in different -- For instance, say, our company would use a cleaning protocol, different cleaning protocols, depending on the product and the process and the equipment used. So we are not going to come up with a standard bottom line, you have to do this, and be practical. The regulation would have to be based on product to product to product.

CHAIRPERSON PRIOLA: Dr. Baron?

DR. BARON: Thank you. Hank Baron. I was just going to say something along those lines. I think personally, instead of imposing a standard for these kinds of decontamination procedures, as you see

from the data that's been presented today and also from Dr. Scott's presentation, a lot of this work is context specific.

So I think it would be better for individual companies to evaluate their conditions and demonstrate their ability to inactivate to the agency rather than try to impose a single set of standards, which might not be practical throughout the industry. Thank you.

CHAIRPERSON PRIOLA: Okay. So regards to question 2 then -- Well, let me ask FDA, in terms of this issue, I had forgotten about this issue of variation between manufacturing processes. When you say in question 2, are the available scientific data sufficient for FDA to recommend specific methods for cleaning, is that for every manufacturer's specific methods for cleaning, or is there -- I don't -- Given this variation in the manufacturing processes?

DR. SCOTT: It wouldn't be a simple matter. So it wouldn't be saying everybody use 1.0 Normal sodium hydroxide in all of your stainless steel tanks. It would have to really be -- It would be, certainly, more than likely in the form of guidance, if anything, and it would take into account the range of needs and contexts that would be there. So --

CHAIRPERSON PRIOLA: Dr. Bracey?

DR. BRACEY: Yes. I just had a question. Is the minimum -- and this may not be known, but what is the minimum now? Is it 4 Logs, 3 Logs? What's the lowest clearance that you have? If, in fact, the minimum is currently 4 Logs, and I think that would speak to the lack of a need to, in essence, impose a standard now, because products -- You may have some that are 8 Logs, but you're really not going to have that much contamination, I think, with these products.

DR. SCOTT: I think you are asking about clearance during the manufacturing process, and we don't have all the information from all of the companies using scaled down models with TSE infectivity or some surrogate readout for TSE. However, I can tell you that very often many products seem to have at least one method that will eliminate in the 3-4 Log range -- or one process, but I cannot tell you that across the board, and there are a few that may not.

CHAIRPERSON PRIOLA: Dr. Edmiston.

DR. EDMISTON: When I think of the presentations we've had over the past two days, there has been substantial data which has discussed the inactivation of these particles on inert surfaces. Of

course, we are talking about low risk tissue.

The information that is somewhat onerous for us to actually reach an agreement on was based on a high risk tissue, critical tissue or critical devices. I think this is much more simplistic in that we are dealing with low risk tissues, and we know -- We know what inactivation occurs on inert surfaces, be them glass, polystyrene or stainless steel, from the presentations that we've had with the known chemicals that are currently available.

So I think there is data there that addresses that type of response for low risk tissues on inert surfaces.

Let me just get clarification of this, because sometimes I'm wrong. Dr. Weissmann, did I make the appropriate interpretation in terms of what I just said?

DR. WEISSMANN: Yes, except that, in fact, we did not sterilize plastic.

DR. EDMISTON: All right.

DR. SCOTT: I'd just like to add another point, and that is, in spite of the fact that these are low risk tissues, there are products which are used throughout the lifetime of people with immune deficiency or hemophilia. So you need to also account

for the lifetime dosing, as it were, of a person. So even potentially small amounts of infectivity eventually would be a worry.

CHAIRPERSON PRIOLA: Dr. Bailar?

DR. BAILAR: The question is in terms of whether the available data are sufficient for FDA to recommend specific methods. I would feel more comfortable in voting on something that is rephrased to say would it be wise or would it be appropriate for FDA to recommend specific methods. It isn't quite the same thing.

CHAIRPERSON PRIOLA: What do you mean by appropriate? I mean, it's the FDA's purview to do this. So what do you mean by appropriate?

DR. BAILAR: Well, I can imagine that we would conclude, yes, the data are sufficient for FDA to recommend specific methods, but that isn't a good thing to do.

CHAIRPERSON PRIOLA: Which isn't a good thing to do, for FDA to recommend a specific method? I don't understand.

DR. BAILAR: I'm a little concerned about having FDA recommend specific methods at this point in the development of the science.

CHAIRPERSON PRIOLA: And I think that is

partly what A and B address, but maybe Dr. Epstein can clarify this.

DR. EPSTEIN: Well, in terms of how we phrase our questions, you know, we ask to be advised on the science, and we generally, you know, arrogate to ourselves the policy decision. So that's why it is phrased the way it is.

You know, if you think the science is not mature, we get the message. It would be unwise to move forward with policy. But we are asking to be advised scientifically.

CHAIRPERSON PRIOLA: Dr. Gambetti?

DR. GAMBETTI: The problem I have, and maybe others have, is that here we are asked to give a very specific recommendation, to make a choice. And although we have heard a lot of presentations and we receive a tremendous amount of information, I wonder whether one can do this recommendation without, like we are asked now, really digesting and review all this information that we receive in a more critical way before making such a specific recommendation that is based on technical information.

In other words, we are required to not only have digested, listened to, digested all the presentations, but also to be in a position to

evaluate them without having had time to really read them carefully and think about it.

Maybe my brain is slower than others', but that is the way I would proceed, rather than being kind of forced to give -- to make a decision just on the basis of this tremendous amount of information and not time to evaluate it and think about it.

CHAIRPERSON PRIOLA: In one way, having voted -- I guess I keep coming back to question 1, saying that right now what they are doing is adequate. In one way, we have decided that the cleaning with the sodium hydroxide is adequate to protect against this low risk tissue presently.

So maybe we don't have to get more specific than that, that we could say we think some of the data -- If we say the data is sufficient, would we recommend moving along the same lines as what they are doing now? I don't know if we need to be more specific than that, because I agree. I can't -- We can't pick and choose. Dr. Scott?

DR. SCOTT: Well, I think that we've heard some very useful discussion on this question, and it wouldn't be essential for us to have a vote on it. We do understand the difficulties of doing that at this point.

CHAIRPERSON PRIOLA: Dr. Gambetti?

DR. GAMBETTI: We can vote on that.

CHAIRPERSON PRIOLA: Can we vote on that, yes. Thank you for letting us off the hook. Everybody seems very relieved. Dr. Baron.

DR. BARON: I would just like to add that the study -- the collaborative study coordinated by the PPTA, which will be covering really the whole range of the two solutions which are most widely used, is going to address a lot of these questions. So perhaps this question should be reasked at some point in the future when the data starts coming in from this study.

CHAIRPERSON PRIOLA: Actually, someone here on the Committee had mentioned that earlier, and I think that is a really good point, that that study is starting to get underway and can be used as a basis for making these specific recommendations.

So I have a sense that the FDA has gotten out of the discussion what they want and realize the hesitation for making these specific recommendations. Are there any other comments from the Committee? We are off the hook for voting on number 2, but would anyone else like to contribute anything? Yes, Shirley?

MS. WALKER: Do we need to table it for another meeting?

CHAIRPERSON PRIOLA: Excuse me? Table it for another meeting? Is it required that we do that officially, table it for another meeting?

DR. SCOTT: I think we have a reasonable record of bringing back what you've asked for. So we will attend to that.

CHAIRPERSON PRIOLA: This is true.

Very well. I think that's the end of our agenda, if we are not going to vote on this recommendation. I would like to thank everybody, the speakers for their fantastic presentations, again, of presenting both published and unpublished data, which I think is tremendously generous.

Thank the members of the Committee for being so patient and paying attention. We are adjourned. Have a good trip back.

(Whereupon, the foregoing matter went off the record at 3:46 p.m.)