U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICAL EVALUATION AND RESEARCH

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TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

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16th MEETING

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THURSDAY,

OCTOBER 14, 2004

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The Committee meeting was held in the Hilton Hotel, 8727 Colesville Road, Silver Spring, Maryland, at 8:00 a.m., Dr. Suzette A. Priola, Chairperson, presiding.

PRESENT:

SUZETTE A. PRIOLA, Ph.D., Chairperson

JAMES R. ALLEN, M.D., Temporary Voting Member

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

VAL D. BIAS, Member

ARTHUR W. BRACEY, M.D., Member

LYNN H. CREEKMORE, D.V.M., Member

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

PRESENT (Continued):

PIERLUIGI GAMBETTI, M.D., Member

R. NICK HOGAN, M.D., Ph.D., Member

ALLEN L. JENNY, D.V.M., Temporary Voting Member

RICHARD T. JOHNSON, M.D., Member

FLORENCE KRANITZ, Acting Consumer Representative

KENRAD E. NELSON, M.D., Temporary Voting Member

STEPHEN R. PETTEWAY, Non-Voting Industry Representative

MO SALMAN, B.V.M.S., M.P.V.M., Ph.D., D.A.C.V.P.M., F.A.C.E., Temporary Voting Member

JAMES J. SEJVAR, M.D., Temporary Voting Member

WILLIAM FREAS, Ph.D., Executive Secretary

FDA REPRESENTATIVES:

DAVID ASHER, M.D.

STEVEN ANDERSON, Ph.D., MPP

JAY S. EPSTEIN, M.D.

JESSE L. GOODMAN, M.D., MPH

DOROTHY SCOTT, M.D.

ALAN E. WILLIAMS, Ph.D.

INVITED SPEAKERS:

HENRY BARON, M.D.

LAWRENCE ELSKEN, D.V.M.

INVITED SPEAKERS (Continued):

LISA FERGUSON, D.V.M.

PETER GANZ, Ph.D.

LUISA GREGORI, Ph.D.

BURT PRITCHETT, D.V.M.

ROBERT G. WILL, M.D.

C O N T E N T S

C O N T E N T S

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

(8:08 a.m.)

DR. FREAS: Good morning. Again, if you'd take your seats, we'd like to get started.

The reason why I'm trying to move this meeting along is some of you watched TV last night and knew that you didn't necessarily have to answer questions. However, of our Advisory Committee members we won't let them go home until they give us full and complete answers to every question we ask.

Good morning. I would like to welcome everybody here. This is the 16th meeting of the Transmissible Spongiform Encephalopathies Advisory Committee.

I am Bill Freas. I'm the Executive Secretary of this committee.

The entire proceedings today will be open to the public, and we welcome public comment during our open public hearing sessions.

I would like to introduce now the members seated at the head table, and I'll start on the right-hand side of the room. That's the audience's right-hand side.

In the first chair we have Dr. Pierluigi Gambetti, Professor and Director, Division of

Neuropathology, Case Western Reserve University.

The next chair is empty right now, but it will soon be filled by Dr. Kenrad Nelson. Dr. Nelson is a former Chair of FDA's Blood Products Advisory Committee. He is also Professor, Department of Epidemiology, Johns Hopkins University, School of Hygiene and Public Health.

In the next char we have Dr. Allen Jenny. He's a pathologist from the National Veterinary Services Laboratory, USDA, Ames, Iowa.

In the next chair we have Dr. James Sejvar, neuroepidemiologist, Division of Viral and Ricketttsial Disease, Centers for Disease Control and Prevention.

In the next chair we have Dr. Nick Hogan, Assistant Professor of Ophthalmology, University of Texas, Southwestern Medical School.

In the next chair we have Mr. Val Bias, Co-chairman, Blood Safety Working Group, National Hemophilia Foundation, Oakland, California.

In the next chair we have Dr. Stephen DeArmond, Professor, Department of Pathology, University of California, San Francisco.

Around the corner of the table we have Dr. James Allen. Dr. Allen will be Acting Chair of FDA's

Blood Products Advisory Committee, and they'll be holding their meeting next week, and the information for that committee is, of course, up on the FDA Website.

Dr. Allen is also President and CEO of the American Social Health Association.

In the next chair is the Chairman of this committee, Chairperson of this committee, Dr. Suzette Priola, investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

Next we have our Acting consumer representative, Ms. Florence Kranitz. She's President and founder of the CJD Foundation, Akron, Ohio.

Next we have Dr. John Bailar, Professor Emeritus, Department of Health Studies, University of Chicago.

Next we have Dr. Lynn Creekmore, staff veterinarian, APHIS Veterinary Services, USDA, Fort Collins, Colorado.

Next we have Dr. Mo Salman, Professor and Director, Animal Population Health Institute, College of Veterinary Medicine, Colorado State University.

Next we have Dr. Arthur Bracey, Associate Chief of Pathology, St. Luke's Episcopal Hospital, Houston, Texas.

Next we have Dr. Richard Johnson, Professor of Neurology, Johns Hopkins University.

At the end of the table, we have our non-voting industry representative, Dr. Stephen Petteway, Director of Pathogen Safety and Research, Bayer Corporation.

I would like to welcome everyone for attending this meeting this morning.

I would now like to read into the record the conflict of interest statement required for this meeting.

The following announcement is made part of the public record to preclude even the appearance of a conflict interest at this meeting. Pursuant to the authority granted under the committee charter, the Director, Center for Biologics Evaluation and Research, has appointed to this meeting the following participants as temporary voting members. They are Dr. James Allen, Allen Jenny, Kenrad Nelson, Mo Salman, James Sejvar, and Ms. Florence Kranitz.

Based on the agenda, it has been determined that the committee will not be providing advice on specific firms or products. The topics being discussed by the committee are considered general matters issues.

To determine if any conflicts of interest exist, the agency reviewed the agenda and all relevant financial interests reported by the meeting participants. The Food an d Drug Administration prepared general matters waivers for participants who required a waiver under 18 U.S. Code 208.

Because of the general topics impact on so many entities, it is not prudent to recite all of the potential conflicts of interest as they apply to each member. FDA acknowledges that there may be potential conflicts of interest, but because of the nature of the discussions before the committee, these potential conflicts are mitigated.

We would like to note for the record that Dr. Stephen Petteway is a non-voting industry representative for this committee acting on behalf of regulated industry. Dr. Petteway's appointment is not subject to 18 U.S. Code 208. He is employed by Bayer and thus has a financial interest in his employer and other similar firms.

In addition, in the interest of fairness, FDA is disclosing that Dr. Petteway is a member of the Viral Safety Working Group at the Plasma Protein Therapeutics Association.

With regards to FDA's invited guest

speakers, the agency has determined that the service of these speakers are essential. The following interests are being made public to allow participants to objectively evaluate any presentation and/or comments made by these speakers.

Dr. Lawrence Elsken is employed by the USDA Veterinary Services in Ames, Iowa.

Dr. Lisa Ferguson is employed by the USDA Veterinary Services in Hyattsville, Maryland.

Dr. Peter Ganz is employed by the Biologics and General Therapies, Director of Health Products and Food Branch, Health Canada.

Dr. Luisa Gregori is employed by the Baltimore Research and Education Foundation, a nonprofit organization. She is doing research on TSE diagnostics and TSE removal.

Dr. Robert Will is employed by the National CJD Foundation Unit in Western General Hospital in Edinburgh, U.K. He also consults and advises with a firm that could be affected by the committee discussions.

In addition, there are regulated industry and other organizations scheduled to speak at today's hearing. These speakers have financial interests associated with their employer and with other

regulated firms. They were not screened for these conflicts of interest.

Members and consultants are aware of the need to exclude themselves for discussions involving specific products or firms for which they have been screened for conflicts of interest. Their exclusion will be so noted in the public record.

With respect to all other meeting participants we ask in the interest of fairness that you address any current or previous financial involvement with any firm whose product you wish to comment upon.

Waivers are available upon written request by the Freedom of Information Act.

That ends the reading of the conflict of interest statement. Before I turn the meeting over to our Chair, I would like to ask you if you have a cell phone, would you please check to make sure that it's in the silent mode? Your neighbors would appreciate that.

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

CHAIRPERSON PRIOLA: Thank you, Bill.

I'd like to welcome everybody, all the members of the committee, the temporary voting members

of the committee.

Since we have a very full schedule today and a set amount of time to get things done, I'd just like to begin by turning it over to Dr. Jesse Goodman.

DR. GOODMAN: Well, good morning. I ran over here, and it's my pleasure really to honor the people who have helped us on this committee because it's important. Certainly CBER Advisory Committees are critical for us in receiving expert advice, in having a public forum, and in having a transparent process, and these kinds of tremendous public health responsibilities I think are nowhere more obvious than with TSE and some of the kinds of issues you consider in terms of safety of our products here.

It is a lot of work to be on these committees and review the material. It's a lot of responsibility because as we know, there's never an easy answer to any of the questions we look at, and I notice the agenda today, and I've been helping to look at the materials that folks have put together; that this is no exception. It's extremely challenging to use the best science to do public health while you're running 40 miles an hour at the same time and accumulating new data.

So really this morning I just want to

honor those who have provided a service to this committee, and I'd like to ask Dr. Priola and John Bailar, Steve Petteway, Pierluigi Gambetti, and Stephen DeArmond to come up and join me at the microphone.

My understanding is that all of you have served for about three years on the committee. So that is a real contribution not just to FDA, but to the people of this country. So please join me in thanking these folks for that and honoring them with a plaque and, I believe, a letter from our Associate Commissioner for External Affairs, External Relations, Sheila Walcoff.

So again, please join me in honoring these folks who have contributed so much.

(Applause.)

(Whereupon, the plaques were distributed.)

DR. GOODMAN: So, again, thanks, everybody.

(Applause.)

DR. FREAS: We did have a photographer, and we may call you back during a break for a picture, but the photographer apparently is not at the correct hotel.

Thank you.

CHAIRPERSON PRIOLA: Okay. Thank you very much, Dr. Goodman.

Speaking for myself, it has been a real pleasure and privilege serving on this committee, and I have learned a lot from doing so, and I think that's true of everybody else here.

I think we should go ahead and get started with the informational presentations. I just want to remind the committee that these are informational presentations for our use only. It is really not a voting topic. These aren't discussion topics. This is just to sort of update the committee on the state of things in the testing world today primarily.

So what I'm going to do is have the speakers give their talks and save the questions to the end in order to try to keep to time.

So our first presentation is from Dr. Lawrence Elsken from the USDA.

DR. ELSKEN: Well, good. That wasn't a very good start the first time around anyway.

The relationship between license test kits and enhanced surveillance is that the test kits are being used to increase the throughput and to provide the enhanced surveillance that's ongoing at this time.

Just since I was first up, I thought I'd

briefly do the prions or abnormally folded proteins, not a virus or bacterial. There is no known host immune response. However, you can produce antibodies across species. So there are polyclonal and monoclonal antibodies, which is an essential component of the kits.

There's two forms of the prion protein, the normal, the PrPc on most cells, although high concentration in neural tissue, and then the infectious form, which is relatively resistent to disinfectant, sterilization, and proteinases, and accumulates and kills neural cells.

There's at this time no effective live animal test for BSE. All the tests currently use brain tissue, neural tissue. The first and gold standard test is immunohistochemistry, IHC, which combines histopathology with an antibody demonstration of the presence of a proteinase-resistant protein.

Negative tests do not guarantee the absence of infectivity, and the tests are not intended as a food safety test. So the histology, immunohistochemistry is basically an ELISA where the fixed tissue is reactive with an antibody to PrP. The tissue has been treated to remove the proteinase susceptible normal form, and then there's an antibody

precipitate on the slide.

The rapid tests are in various formats, enzyme linked immunoassay, ELISA, EIA and Western blots. The rapid tests are generally more rapid. They are associated with occasional false positive initial reactions, especially in the ELISA. The Western Blot test of the rapid test has a lower throughput, is slower, and is more involved than the ELISA. It provides another measure of confirmation that what you're looking at is the infectious prion on a size basis, and it provides some information on possible variants of BSE, and there are some recent publications on that coming from Europe and Japan.

All of the approved tests have excellent sensitivity and specificity, but they are only intended as screening tests, and I think I say that twice more on upcoming slides.

The immunohistochemistry I think I've already mentioned adds the immunologic confirmation, and it can have positive results before you're getting some of the classic spongiform lesions, and basically it is our gold standard test so there can be no false positives. Again, it can be negative and experimental inoculations. It generally requires several days to complete the test.

And the lower section you can grossly see that the blue is the normal and then the pink is where there is a precipitate reacting with the abnormal protein.

This is just to let you know, well, we'll let industry know and the general scientific public and the public in general that, yes, we will consider licenses for rapid tests for BSE as a disease of animals at the Center for Biologics.

So a brief background on why the USDA is licensing these kits is all veterinary biologics are regulated and reviewed and licensed by the USDA. Veterinary biologics include diagnostic test kits intended for use in the diagnosis of disease in animals, and just our authorizations.

So what makes a regulated test? Because we do not regulate reagents or media or bacterial growth or things like that.

The diagnostic test kit contains all the reagents required to do the test, complete instructions for the test, instructions to interpret the test, and claims, uses and limitations. They're used to diagnose the existence of disease usually, although there are some tests coming on to indicate susceptibility to disease agents, and as I said,

reagents are not regulated.

Our pre-license assessment includes accuracy and precision, diagnostic sensitivity, specificity. The ruggedness and repeatability gets into to demonstrate that at various labs it will produce consistent results, and in the prelicense process, you're generating the predictive diets (phonetic) for the test.

So the prelicense validation involves testing large numbers of known positives and negatives. These are general slides just on diagnostic test kits. So there aren't antibody test kits for the TSEs, but just in general this is the format that we're looking at companies to follow, and the gold standard in the BSE test has been immunohistochemistry.

The problem, if you will, with the TSEs and using neural tissues is that unlike a serologic test where you can have animals and do repeat sampling, you only get one sampling per animal on the TSE test kits. So we have a little bit of problem with that second point determining the onset of detection of disease.

The manufacturing controls is to minimize within serial. So bottle to bottle and serial to

serial variation. There's controls on the method of production. There's controls on the inputs that are used to produce the test kits, and there's a serial release process that we maintain in the USDA where each batch, lot or serial of product needs to be submitted to the USDA for testing and then released after that testing.

And the TSE test kits licensed by the USDA are all in 100 percent confirmatory testing. So we'll be testing them as long as I can see.

And the serial test panel is usually generated by the USDA for use in these test kits by all manufacturers. So there's a standardization there.

We're also inspecting the manufacturing facilities. We do some more extensive prelicense testing of the serials and the seeds and the materials that go into the product, and we review and approve all labeling.

We have a slightly different terminology for foreign manufacturer versus domestic manufacturer. Foreign manufacture kits are issued permits, and there's a responsible U.S. party. We've issued three permits for BSE test kits to Bio-Rad, France, Abbott Laboratories for Enfer, Enfer's polyclonal ELISA.

That's the only polyclonal product of the seven that are licensed. And the Roche is a permittee for Prionics, Switzerland.

There's four U.S. manufacturers that have been issued licenses. IDEXX is an immunoassay. Pierce, which is basically producing the Prionics kit, has sublicensing the situation. And Pierce is also manufacturing and exporting basically the Prionics kit back to Europe as a manufacturer.

And then VMRD in Washington State has an export only immunohistochemistry kit. Canada evaluated that and reported on that a few years ago.

Okay. So for the format of the technique, all use obex tissue. You purify the normal or abnormal, and abnormal together PrP protein. There's a treatment to remove it. It's removed in an immunologic sense. So it might be denatured. It might be digested with proteinase. So that the normal PrP will not react anymore with the antibody that's used as an indicator for the presence of the abnormal.

The Western Blot adds an additional step to separate protein basically by molecular weight, transferred to nitrocellulose, and then react with the antibody to the PrP. And then you develop the color.

Diagnostic Center development, there's a

lot of things being done. Of course, the ultimate goal always seems to be a "cowside" or an animal-side test that will give you an answer in about a millisecond.

So this just basically has got a Website on there. If you have additional questions or would like some more information, it's available there.

The enhanced surveillance program or expanded surveillance program began June 4th, 2004. The purpose is to determine if BSE is present in the United States and to determine if risk management policies are adequate, but it is for animal health and not food safety.

Guiding our decision of what animals to test, and our risk analysis has been the experience in the European Union. As you can see, the emergency slaughter, that EM slaughter category is about 1,000-fold more positive animals than the healthy adult cattle as far as percent positive on test.

And, again, the suspect category is astronomical.

So the experience has demonstrated that targeting surveillance efforts at certain high risk populations is the most effective way to identify BSE. Estimates that the U.S. high risk population is about

446,000 cattle. These are further broken down into about 246,000 on-farm deaths with unexplained causes or causes consistent with BSE in a population that's consistent with the possibility of being positive for BSE.

Two hundred thousand ante-mortem condemnations, and then your highest risk would be your foreign animal disease investigations for CNS diseases where there's reason to believe in an adult cattle.

So the majority of the samples for the enhanced surveillance program are going to be coming from nonambulatory cattle, cattle with CNS disorders, other signs associated with BSE such as emaciation and injury, and dead cattle.

And USDA personnel will also sample all cattle condemned on ante-mortem inspection by USDA's Food Safety Inspection Service.

And the risk analysis is basically the outcome of that, is that if we sample about 250,000 high risk cattle and no positives are found, then we can be 99 percent confident that there were less than five positive animals in the entire target population.

For the much more extensive background on the enhanced surveillance plan and inferences in the

risk analysis, I provided the Website.

And just to update you as to where we are as of yesterday or earlier this week, no positive BSE test results in the enhanced surveillance program. We did have a not negative ELISA test result that caused a bit of a stir early on in the program.

Cumulative tests are approaching 80,000. We're testing well over 5,000 a week at this point. So we're well on track to get the 280 or so thousand samples within the 18 month goal.

And if you want to see week-to-week updates, we've provided the Website there where those are posted.

And with that I'm finished.

CHAIRPERSON PRIOLA: Thank you, Dr. Elsken.

Our next speaker will be a recently retired member of this committee, Dr. Lisa Ferguson.

DR. FERGUSON: Good morning. Actually that sounds odd, "recently retired." I wish I could retire completely because there's so much more I would like to do, but anyway, glad to be here this morning.

I am going to go over a bit of the world situation in regards to BSE and what some of our response has been to that. Larry and I are also doing

a bit of a tag team on surveillance. So I will hit on, again, a few of the high points of what we've done for surveillance because we recognize there's lots of questions and confusion out there about what we've been doing since June 1st and why.

So let's talk about the entire world situation. Just total cases, greater than 188,000 total cases since the beginning of this entire thing. Just a reminder that the vast majority of those are still found in the U.K., greater than 96 percent. Actually I think it's closer to 97 percent.

If you want to have a fairly up to date Website that lists current reported totals of detected disease, the OIE maintains their Website fairly frequently, and as countries report those numbers, OIE does post those, and that is their Website right there. You can actually get it in English, French, or Spanish. Take your pick.

Just to show you some of the numbers, I realize this is probably a busy slide and too tiny print for folks to see, and I just now realized also the red print doesn't show up real well, does it? Anyway, down there in the lower right-hand corner, the total U.K. cases is close to 184,000. Compare that with all of the rest of the world, which is non-U.K.,

about 5,000. That is, you can see some countries stand out with higher numbers of cases. In general terms, those are countries that found their first cases back in the late '80s, 1989, 1990, with a few exceptions. Some of the European countries that first identified their cases in 2000, 2001 like Spain and Portugal, actually their numbers have climbed up fairly quickly.

The European Union posts very detailed summaries of their test results on an annual basis on their Website, and just to look at their summary testing in 2003. Now, the numbers that I'm quoting here will be for the 15 member states. Their 2003 report also does include some numbers for the ten additional member states that have recently joined the union, but these are just for the EU 15. So they've tested close to 10 million cattle in 2003, and of that, the vast majority were apparently normal health cattle presented for slaughter greater than 30 months of age. So 8.7 million of that were healthy animals presented for slaughter.

Out of that, about 1,300 positive cases. But the significant point is you compare 2003 to 2002. You can also go back and compare to 2001, but their number of cases and their overall prevalence decrease

by about 35 percent as compared to 2002.

Now, prevalence, when I'm using that term, that's number of cases per million adult animals, and that's detectable prevalence. So that does demonstrate that the control measures that they have put in place do seem to be having some effect.

And let's look a bit and pull out just a few countries just to do some comparison. So the total estimated adult cattle population in the EU 15, about 39 million. Out of that, you know, 1,300 positives. So that's a prevalence of about 35 percent. Compare that to 2002, which was 53.

But you look at individual countries. The numbers are slightly different. As you can see, let's look at France. With a higher cattle population, close to 11 million, 138 positives in 2003, and their prevalence is still decreasing.

Portugal actually is interesting. Their prevalence seems to be increasing a bit. The U.K., prevalence continues to decrease dramatically every year.

We talk a bit about country status and how different assessments of country status have been done. There is a wide variety of those out there. One of the most commonly talked about and known is the

European Union has done what they call geographical BSE risk assessments, or GBR. This was actually initially started in 1998 under the auspices of the Scientific Steering Committee.

They completed that initial round of assessments in 2000 still under the SSC, and the way this methodology was set up, it categorized countries into one of four levels, Level I being BSE is very unlikely to occur; Level IV being BSE occurs at a high incidence.

At that point in time, the U.S. was considered GBR, Level II in 2000.

The commission requested that several reassessments be done. They didn't redo all of the assessments that they did initially in 2000. I think they are in the process of redoing quite a few more of those primarily due to additional findings of BSE in additional European countries and elsewhere in 2001 and later.

These recent assessments have been done not under the auspices of a Scientific Steering Committee. That committee is no more, but it's now under the auspices of the European Food Standards Agency. Hopefully I got that right. I always get it mixed up.

Anyway, in this initial or reassessments recently, U.S., Canada and Mexico, all of North America, has been put in Level III. South Africa also was put into Level III. Interestingly enough, our Australian colleagues, they remain at Level I, and I'd encourage folks if you're interested in reading some of those and doing some comparisons, it's actually very interesting to see how those conclusions were reached.

You can rad their entire report. It's posted on their Websites.

Level III actually is BSE is likely to occur or occurs at low incidence level.

Now, the OIE, which is the world organization for animal health, also has guidelines for evaluating country status, and they have five categories of countries: free, provisionally free, minimal risk, low incidence and high incidence, and the OIE a couple of years ago offered the opportunity for countries to submit information, and the OIE would put together an ad hoc panel to review this information and determine if countries could be considered free or provisionally free.

Several countries submitted information, and there were some questions, some concerns raised

with the initial assessments, and they have kind of redone the process a bit. They did finalize that process for four of those countries, and at last May's general session officially recognized four countries as provisionally free: Argentina, Iceland, Singapore and Uruguay.

Now, there were some countries that initially put some information in, but pulled out of the process and didn't finish the process. So just to make the point with the OIE, that is determinant on a country sending in information and specifically requesting that that be considered.

So what has USDA-APHIS done in regards to any of these reports of disease? Various things. Our import regulations are contained in Title IX, Code of Federal Regulations, Parts 93 to 98. Specifically probably of interest to this committee, Part 9418 contains what we call the BSE restricted list. These are those lists of countries that are either affected with BSE or that we consider to present an undue risk of BSE.

After Canada found their first case in May 2003, we did put Canada in that list of countries affected with BSE.

In November of last year, we did publish

a proposal to change this section of the regs. along with other sections of the regs., but our proposed rule essentially was creating another categories, a minimal risk category of BSE. The proposal outlined import conditions for certain animals and products from countries that would be in that minimal risk category. We also proposed placing Canada in that category.

That comment period was open until after the first of the year. After the finding of the case in Washington State, we let the initial comment period expire. We then reopened that comment period this spring. It is closed again.

We have more than 3,300 comments, some very substantive comments that we're continuing to review and analyze, but this is a priority for us to somehow finalize this regulation here in the near future.

A brief summary of the Canadian situation. As everybody knows, two indigenous cases identified. The case in May 2003, and then the cow that stole Christmas, the December 2003 case actually diagnosed in Washington, but this cow was confirmed to be Canadian in origin.

They've done extensive epi investigations

on each of these and have taken additional measures; as probably folks know, in June 2003, did institute SRM removal in the human food chain.

They have had a feed ban in place since 1997 essentially the same as ours and put in place at the same time. As we are, they are also considering additional animal feed restrictions at this point.

They have instituted increased surveillance. As we have done, their surveillance has traditionally been targeted at high risk animals, and their goal is to obtain 8,000 samples here in 2004, and they're ramping up their surveillance and hope to then obtain about 30,000 samples in 2005.

And with comparing adult cattle populations essentially it would be considered equivalent to the efforts that we're trying to do. They are on track for their goal in 2004 with more than 6,300 samples today.

The committee has heard a lot of this information back in February, but just to summarize again, actions that our colleagues in FSIS have taken for public health preventive measures in response to the North American situation. These were all published in the Federal Register in January 12th as interim final rules or as policy notices.

Essentially, prohibit nonambulatory, disabled animals for human consumption. These animals are contemned on ante mortem inspection. Specified risk materials prohibited from the human food chain. Mechanically separated meat prohibited from human food and also have additional process controls on advanced meat recovery product, and if samples are taken from animals presented for inspection for our BSE surveillance, that carcass is not passed for inspection until negative test results are received.

And then just to hit a few high points again, on our surveillance plan, I can't stand not to talk about it. As Larry has said, our goal is obtain as many samples as possible from the targeted high risk population in a 12 to 18 month period. We did get started on June 1st, and we are targeting the population where disease is most likely to be diagnosed, and this is the most efficient way to find the disease if it is present in the U.S.

Our assumption is if we can't find disease in this targeted population or the most likely population, we would be even more unlikely to find it in the non-targeted population or the healthy animal population.

We will be able hopefully to use the data

that we obtained to extrapolate the information to the broader cattle population. There are several different ways to do that. We're looking at lots of different options to be able to do that, but what we can take is, okay, the statistic that Larry quoted: if we get 268,000 samples, we'll be able to say, okay, in this targeted high risk population, that means there's no more than five cases in that population. Then we can extrapolate that to the broader either adult cattle population or entire cattle population, depending on how you want to do it.

Just again a summary of what our targeted population is and those entities that we're working with to obtain this. I would like to emphasize there still seems to be a lot of confusion out there that people think an inspected slaughterhouse is the only place where we can have access to these animals.

There are lots of the animal disposal chain with rendering facilities, dead stock facilities, non-inspected slaughter facilities, salvage slaughter facilities. We've been working with these type of facilities all the way along, and that's where our targeted population generally shows up. These are the animals. They're not clinically normal, apparently healthy looking animals.

So we're working with these other facilities. These are nonambulatory animals, animals that die on the farm for unexplained reasons, any type of field central nervous system cases or on-farm suspects.

We work with veterinary diagnostic labs as they get odd neurological cases, other cases that might fit a clinical picture, working with the public health laboratories. As they get rabies negative samples, they can forward those tissues on to us, and then as Larry mentioned, we are working with our colleagues in FSIS and all the animals that are contemned on ante mortem and slaughter are sampled.

Just to emphasize where we've been in the past and where we are now, these are summary charts through the end of May of this year, and the past two years we are looking at approximately 20,000 samples a year. Up through May of this fiscal year we had a bit more than 17,000 samples.

Just to show you what populations those were coming from in the past, primarily dead stock downers. The yellow line are the total samples. The purplish line were those nonambulatory animals, and the blue line were dead stock.

Just our numbers again. Total numbers

conducted since the start of June through October 10th. All of these have had negative results. We did have two inconclusives on the rapid screening tests. If they get a reactive test, those samples are immediately forwarded to our National Veterinary Services Laboratory for confirmatory testing. They are deemed to be inconclusive on that initial rapid screening test.

Confirmatory testing is done then with immunohistochemistry or Western Blot, depending on what type of tissue we have.

And just to show you our graph that shows we are making progress, these are tests conducted per week. What we've tried to project is to reach our goal we need to be at about 5,000 samples a week at a sustained level, and we've been at that level with a little minor glitch there over holiday weekends since essentially the first part of October.

So we feel like we're doing really pretty good, and we're on track to meet our goal, and hopefully we'll have some very good data to analyze here in about a year.

We do have lots of information up on our Website. I'd encourage folks to read through that, and if you've got questions, let us know.

Thank you very much.

CHAIRPERSON PRIOLA: Okay. Thank you, Dr. Ferguson.

The last speaker for this informational portion will be Dr. Pritchett.

DR. PRITCHETT: Good morning. I'm Burt Pritchett with the Division of Animal Feeds and FDA's Center for Veterinary Medicine.

Before I update the committee on the status of our efforts to strengthen the BSE feed regulation, I would like to just briefly review the feed ban that is currently in place.

The current feed ban went into effect in 1997. It prohibits feeding mammalian protein with some exceptions to ruminant animals. Those are exceptions are blood and blood products, milk and milk products, gelatin, porcine or equine material that has been obtained from a single species slaughter facility, and plate waste.

In addition to prohibiting the use of mammalian protein and ruminant feed, the regulation requires that those firms that handle prohibited material and also make ruminant feed for feed ingredients intended for ruminants, either maintain separate equipment or facilities or else use clean-out

procedures adequate to prevent cross-contamination.

It requires that records be maintained sufficient to track prohibited material throughout receipt, processing, and distribution, and it requires that products that contain prohibited material be labeled with a caution statement "do not fee to cattle or other ruminants."

FDA's latest action to strengthen the feed ban was to publish an advanced notice of proposed rulemaking jointly with SUDA on July 14th, 2004. In the ANPRM FDA announced its intention to propose banning SRMs from animal feed.

FDA also asked for public comment on feed controls recommended by the international review team. This is the subcommittee of the international BSE experts convened by the Secretaries, Foreign Animal and Poultry Disease Advisory Committee, and we ask for comments on other new feed control measures being considered by FDA.

The comment period for FDA's questions closed on August 13th. The feed controls recommended by the international review team were that, one, all SRM should be excluded from all animal feed, including pet food; that cross-contamination should be prevented throughout the feed chain, including transportation

and on the farm; and that the current feed ban should be extended to exclude all mammalian and poultry protein from all ruminant feed.

With respect to a ban on SRMs in animal feed, FDA asked for comment on the following. Should the list of SRMs prohibited in animal feed be the same list that's now prohibited in human food?

What portion of the intestine should be considered SRM?

What are the economic and environmental impacts of an SRM ban?

And what methods can be used to mark materials that contain SRMs and what methods can be used to verify non-feed disposal?

Dead stock and nonambulatory, disabled cattle, also known as downers, are among the highest risk cattle population. So an SRM ban would exclude these two categories from being rendered for us in animal feed.

In the ANPRM, FDA asked for information on the economic and environmental impact of banning deads and downers. We asked if SRMs can be effectively removed from deads, and we asked what methods could be used to verify that feed does not contain rendered material derived from dead stock.

In addition to the information requested on SRMs, FDA asked what the risk reduction would be and what the economic and environmental impacts would be of other new feed measures being considered. These other measures include requiring that equipment and facilities used to handle prohibited material be dedicated to the production of non-ruminant feed; removing the exemptions in the current feed ban for blood and plate waste; prohibiting the use of poultry litter in ruminant feed.

We asked if tallow derived from rendering SRMs and dead stock poses a significant BSE risk, if the insoluble impurities level is less than 0.15 percent, and we asked what would be the risk reduction and the economic and environmental impacts of the IRT's recommendation to ban all mammalian and avian meat and bone meal from ruminant feed.

FDA also asked for views on whether these other feed controls are needed if SRMs are banned from animal feed.

As announced in the ANPRM, FDA is focusing first on a proposal to ban SRMs from animal feed. CVM has completed review of those comments that pertain to an SRM ban. Approximately 1,500 individuals and groups took the time and effort to express their views

and provide substantive information which we very much appreciate.

Approximately 1,400 of those were from individuals, mostly form letters. One hundred were from groups. These were primarily trade associations and individual firms in the meat rendering and animal feed industries, livestock associations, consumer groups, state Departments of Agriculture, and other regulatory agencies.

The agency is still working on the proposed rule to remove SRMs from animal feed, and I don't know what the time frame is for publication of the proposal. Once work is done on the proposal, CVM will review the comments that address the other beef controls being considered.

Banning SRMs from animal feed is much more complex both from a regulatory perspective and an industry perspective than banning SRMs from human food because it requires new infrastructure for sorting, transportation, disposal, and regulatory oversight.

Recognizing that this infrastructure might be lacking, the international review team said in their report that a staged approach might be necessary for implementation.

These diagrams help illustrate the

infrastructure challenges starting here with how slaughter byproducts are currently disposed of in the U.S. Estimates used are from the environmental assessment that accompany FDA's interim final rule on use of materials derived from cattle in human food and cosmetics.

Slaughter data from 2003 show that we slaughter 28.2 million steers and heifers that go to slaughter at a young age, and 7.1 million older beef and dairy cows plus a small number of bulls in the older animal category.

Both types of slaughter combined generate about 15 billion pounds of inedible byproducts. This material goes to inedible rendering where it's rendered into fats for industrial and feed use and meat and bone meal which is used in feed for nonruminant species.

The USDA and FDA interim final rules published in 2004 identified as SRMs, tonsils and small intestine from young animals, and brain, skull, eyes, trigeminal ganglia, spinal cord, and the vertebral column, including the dorsal root ganglia, from older animals.

Excluding these tissues from human food did not substantially change the disposal of this

material and did not require new infrastructure because the tissues are eligible to be rendered for use in feed for non-ruminant species.

Besides the slaughter byproducts, cattle mortalities, including some of the downers no longer eligible to go to slaughter also go to rendering. We have some differences in the estimates here which I will explain, but according to the estimates that FDA used in the environmental assessment, the combined cattle mortalities from those under 30 months of age and those over 30 months of age adds another .7 billion pounds of material that goes to inedible rendering.

Not all cattle mortalities are collected by the rendering industry. What is not collected by renderers is disposed of by various other means, mostly by on-farm burial, composting or landfill.

There is general agreement on the estimates of the number of cattle mortalities in the U.S. However, estimates from Informa Economics, formerly the Sparks Company, say that renderers collect around 50 percent of the mortalities rather than the 20 to 25 percent estimate used by FDA, and that's indicated in the footnote there.

According to Informa estimates, an

additional 500 million pounds is rendered rather than being buried or composted on the farm or landfilled. So using Informa estimates, about 16.2 billion pounds of cattle mortalities go to rendering and about 1.5 billion pounds goes to other disposal.

Assuming that an SRM ban gets proposed as a full SRM ban, we would still have 13.5 billion pounds of inedible byproducts going to rendering for non-ruminant feed.

I say full SRM ban because we received numerous comments suggesting that we require removal a subset of SRM tissues to remove a percentage of the potential infectivity at a fraction of the cost. For example, remove about 90 percent of the infectivity by requiring removal of brain and spinal cord only from cattle over 30 months of age.

Diverting the human list of SRMs from all animal feed will necessitate special disposal of 1.4 billion pounds of material no longer eligible to be rendered for animal feed. This is composed of tonsils and small intestine weighing 28 pounds, from 28 million head or 804 million pounds, and the longer list of SRMs from older cattle weighing 88 pounds from 7.1 million animals for 624 million pounds.

In addition, a full SRM ban would require

that the .7 billion pounds of cattle mortalities also diverted to special disposal, assuming that the SRM ban does not alter the proportion of deads that were disposed of by rendering. This brings the total volume of material going to special disposal to 2.1 billion pounds.

Options usually mentioned for non-feed disposal are landfill or rendering for volume reduction and then landfill, incineration, alkaline digestion, or biofuel productions.

So this is a brief overview of the challenges of putting an SRM ban in place. There's a lot of work to be done, a lot of details to be worked out before a final rule can be published and an SRM ban can be implemented.

CHAIRPERSON PRIOLA: Okay. Thank you, Dr. Pritchett.

Are there any questions from the committee for any of the speakers this morning: Dr. Elsken -- yes, Dr. Bailar.

DR. BRACEY: Yes. I had a question regarding the testing. There certainly is lots of work that has been done in terms of prelicense testing, but in essence, having the test in the field is somewhat of a different matter, and I assume that

there is a proficiency program that actually tests the performance of the laboratories performing the assay in the field, and I'd just like to get some comment on that.

DR. ELSKEN: Yes. There's an approval process for labs that are using the rapid test. Actually Dr. Jenny could probably talk a lot more about that process, but it involves proficiency panels and, you know, procedures in place.

DR. FERGUSON: Actually before Al jumps in, I'll also add a few more details. At this point we have seven state-federal labs that are working with us. We will be bringing on an additional five labs so that we're not talking a huge number of labs at this point in time.

We did initial approvals in proficiency tests in these labs. We are doing ongoing proficiency testing. We're also looking at their raw data, their OD value, just to see if there's anything that's really funky or off the wall.

Al, do you want to add anything?

DR. JENNY: Well, yeah. We also do inspections of the labs, go visit, check the facility, and look at their SOPs.

CHAIRPERSON PRIOLA: Dr. Gambetti, did you

have a question?

DR. GAMBETTI: In one of the slides presented by Dr. Ferguson, it is entitled "Enhanced BSE Surveillance." It says all negative results, and in parentheses two inconclusives. Apparently it sounds like that if they were inconclusive, they couldn't really be called negative or maybe I don't understand exactly the message here.

DR. FERGUSON: Yeah, okay. My wording probably could have been better. I could have said all negative final results.

We did have two inconclusives on the rapid screening test with confirmatory testing at NVSL. Those were determined to be negative.

CHAIRPERSON PRIOLA: Dr. Bailar.

DR. BAILAR: I have a question for all three speakers, especially Dr. Ferguson, especially with respect to the international data.

Fundamentally about the quality of the data that we've been hearing, there's been a lot of statistical data presented, very simple data, counts, proportions, ratios, and so forth. And I'm wondering about a general sense of the quality of the sampling, the testing that's used, especially in other places; the possibility of covert diversion of sick animals on

the farm; even suppression of evidence.

What level of confidence can we place in the numbers we've heard there?

DR. FERGUSON: I'll jump up and be the first victim.

I think in most instances we can have a pretty good level of confidence in the information. I know especially the European information. They have done quite a bit with testing, quite a bit with legislation and mandating testing.

There are always opportunities for certain ways of diversion, but when you set up a surveillance program, as long as you're maintaining access to a wide variety of challenges or a wide variety of facilities, you should be able to get a good idea and a good, representative sample of whatever population you're looking for.

I think if you look at their numbers, especially from 2001, 2002, and 2003, they are getting a valid sample and getting, I believe, a representative sample.

Mo is looking at me like he might have something additional to say, but I think those numbers are very solid.

I'll go ahead and throw in the Japanese

situation. There are always questions about what's going on in Japan. I'll admit that we have our own set of questions about how they have done surveillance in the past and how they're continuing to do surveillance if it's really meaningful or, you know, trying to get valid information about detectable disease. They've been testing everything presented at slaughter, including veal salves and other animals, which raises questions about how meaningful those tests would be, but they are adjusting that and are doing more sampling in targeted, high risk animals.

CHAIRPERSON PRIOLA: Dr. DeArmond.

DR. DeARMOND: Probably for you, again, Lisa. The question I have concerns who is allowed to test. I don't understand regulations or who can be approved. For example, can the State of California test cattle? How would they be approved to do that, or a boutique slaughter ranch? Could they test to assure that public that their cattle doesn't have, and how could they be approved?

Is it even possible?

DR. FERGUSON: Okay. I'll do part of that, and then I'll let Larry do part of it.

Our policy has been that testing for BSE is done under our auspices and is done in state-

federal laboratories. This is a regulatory disease, and there are certain dramatic actions that would follow. If positives are found, there are certain reporting requirements that are best dealt with in a state-federal animal health regulatory situation.

And I'll let Larry talk about authorities on licensing.

DR. ELSKEN: Well, all of the licenses have been issued with restrictions on distribution, and they are only allowed to be distributed to labs that have been approved by NVSL, and we're inspecting and auditing these records on an ongoing basis.

So I suppose a lab could develop their own immunohistochemistry or histopathology, but on a statewide basis, but I don't know anything about that.

DR. DeARMOND: Could I?

One other question concerns whether strains of BSE have been identified. Is there any way of separating out BSE of Great Britain that is known to be transmissible to human from perhaps some wild type BSE? Any data on that or any way of -- has anyone approached trying to sort out of that problem?

DR. FERGUSON: There are reports of that, and I'm sure other folks sitting around the table can also address this. There are publications from Europe

about atypical strains that are very interesting. Actually these do look different on a Western Blot. You have different molecular characteristics so that you can look at that.

There are still lots of unanswered questions about whether these are truly different strains. You know, are they the same? Are they truly pathogenic? Are they transmissible to people? Do they cause disease even in animals?

Those are all the unanswered questions that are still out there.

DR. DeARMOND: So basically the cases that you've identified in the Untied States, do they match the patterns for the protein as seen in Great Britain?

DR. FERGUSON: Yeah. Actually the two cases, if you look at the blots, et cetera, it does match the pattern in European BSE.

CHAIRPERSON PRIOLA: Hang on just a minute. Ms. Kranitz had a question.

MS. KRANITZ: I apologize if this has already been answered in Dr. Ferguson's talk. I may have missed it, but my question is: what about general random sampling of cattle not falling into the high risk area? Is that being done?

DR. FERGUSON: No, at this point in time

we're focusing our sampling on the targeted high risk population, and that population where we're most likely to find disease if it is present. We're focusing our resources on looking in that targeted population.

CHAIRPERSON PRIOLA: Dr. Johnson.

DR. JOHNSON: Lisa, sorry to keep you on your feet.

DR. FERGUSON: Maybe I'll just stay up here.

DR. JOHNSON: Stay up there. That's right.

Now, particularly relevant to this question of alternate strains of agent, it was particularly interesting in the Italian cases, the two cases from which the different agent, the agent that will be a different strain than the British BSE were from perfectly healthy cattle, but very aged cattle, 15 and 20, as I recall, years of age. They really old, old, retired milk cows.

And if one is looking for other strains, possible even less pathogenic strains, are you going to target that area of looking at the healthy old animals? You didn't mention that in your target population.

DR. FERGUSON: You mean are we going to target that population?

DR. JOHNSON: Yes, in the United States. That's right.

DR. FERGUSON: In the United States?

DR. JOHNSON: That's right.

DR. FERGUSON: Not at this point in time. Our goal is just to try to see, okay, do we have disease here in the U.S., and then if we have some positives to help put parameters around what a possible prevalence level might be. Once we get that first cut, then we'll look at, okay, where do we need to go from there.

DR. JOHNSON: It seems to me that's fine if you're looking for British BSE. If you're looking to say is there other kinds of BSE that occur in the United States, you're not going to answer that unless you look at healthy older animals.

DR. FERGUSON: Well, actually we don't know that. There could be other strains out there in the clinically ill older animals, which is what we're looking at. You know, I don't know that I would necessarily lead to the conclusion that the only way you would find, you know, these strains as in the Italian paper are to look at 15 year old apparently

normal dairy animals. I don't think we have enough information to go there just yet.

CHAIRPERSON PRIOLA: Dr. Hogan.

DR. HOGAN: I just have some simple questions. Who and how identifies the cattle that will be tested? Is it only done by inspectors or is it voluntary by the owners-managers?

DR. FERGUSON: Okay. Some of this gets to the point that I was trying to make about the type of facilities that we're working with, and at this point since our goal is to get samples from as many of the targeted animals as we can, there's not a whole lot of a selection process going on. So if our folks are at a rendering facility, essentially what they're doing is looking to see, okay, is this animal greater than 30 months of age; is it not, and are getting a sample.

So it might be our permanent employees, APHIS employees at these facilities. We've hired a lot of temporary employees. We are working with contractors in some instances. So it's a variety. It is all under our supervision.

DR. HOGAN: How much does one of these tests cost?

DR. FERGUSON: Just the test kit and all affiliated labor and --

DR. HOGAN: Well, like a per test cost. I'm trying to evaluate how much this whole program is costing. You know, is it 50 cents a test or is it five dollars a test?

DR. FERGUSON: No, actually I'll just go ahead and throw out the cost that we have used in our budget figures. For this effort we have obtained 70 million in emergency funds. To run this effort we probably will need some additional funds on top of that.

Now, that does pay for our personnel, equipment, et cetera. We figure our total cost for labor, shipping, the test kit, paying the lab to run the test is about 130 bucks a test. Just literally to the lab, we're paying 12 bucks for a test kit and 12 bucks for the lab to run that kit.

DR. HOGAN: Thanks.

Last naive question. How long from the time an animal is identified until test results are obtained?

DR. FERGUSON: With the rapid test kit we're getting essentially a 24-hour turnaround time. Someone is collecting samples through the day. They pack those up, ship them off FedEx overnight. They're getting results back the next afternoon.

Now, in some instances where there's not an issue with holding the carcass, if that carcass has been buried, going into the landfill, et cetera, we are still running some immunohistochemistry testing as you saw in my slide, and that's not that same turnaround.

CHAIRPERSON PRIOLA: Okay. Dr. Allen.

DR. ALLEN: Let me follow up on that last question just with one brief one, and then I've got another question.

With regard to the 24-hour turnaround, I assume that that's with the screening test only. If it's negatively, obviously that's easy. If it's a presumptive, positive on the screening test, is the animal then removed from the food chain?

DR. FERGUSON: Okay. Yeah, you are correct that that 24-hour turnaround is on the rapid screening test. Let me emphasize that these animals are not going into the, quote, food chain. These are all somehow in the animal disposal end of the industry.

We are holding the carcasses, cold storage, whatever, somewhere, and that carcass remains held. We do offer if we get an inconclusive on the initial rapid screening test, we do offer the facility

that will take care of a disposal form if they don't want to continue to hold it, but that is continue to hold.

If that goes forward on for inconclusive, immunohistochemistry takes probably another four days to a week.

DR. ALLEN: A question for Dr. Pritchett and I guess in light of our recent presidential debate, you know, maybe you can limit your response to two minutes.

(Laughter.)

DR. ALLEN: I think this could take days of discussion.

You mentioned the economic and environmental impacts of some of the additional animal food chain regulations if they're being implemented and the infrastructure is developed and so on. A lot of different players in here and huge economic impacts.

What are some of the different pressures that are bearing on this other than the attempt to use scientific information to make the correct decisions, and how do you see some of this coming out in the long term?

DR. PRITCHETT: Well, you're right. It

would be nice to make the decision purely on a scientific basis. However, my understanding is that for this to go into effect, it's subject to review up through the department level and then to OMB, and at that point, you know, a decision is made on whether this rulemaking is too costly or needs to be trimmed, some of the costs need to be trimmed.

So at that point we may be asked to reduce the cost.

DR. ALLEN: Yeah, thank you.

I think this is an area that needs a lot of open discussion and debate. I think if you were to ask the general public, if you were to lay out for them what all goes into or has in the past gone into animal food products, much less the human chain when we talk about all the processed foods and so on, I think many people would be appalled and public response might drive some of the decisions.

You know, this issue of what's too costly is a total imponderable, and the magnitude of all of this is obviously very difficult. I can't begin to wrap my mind around 15 billion pounds of, you know, SRM or non-SRM foodstuffs, animal body parts that might got into the animal food chain. This is an area that obviously needs a lot of very, very careful

discussion and decision making.

CHAIRPERSON PRIOLA: Okay. We have a couple of final questions. Dr. Salman.

DR. SALMAN: Yeah, this is a question to Dr. Ferguson.

If you could comment about the autolyzed samples, how is that being tested now?

DR. FERGUSON: Okay. Autolyzed samples, actually we've tried to encourage our collectors to do their best to primarily collect viable samples. If we get a sample that is too severely autolyzed to recognize the tissue location, if you're essentially pouring it out of the tube, we're considering that a no test and not running a test.

Now, if we get into a situation where we run and you have a valid sample and you run an initial inconclusive and for some reason then when it's forwarded on to NVSL for confirmatory testing, if you then have an autolyzed sample at that point in time, we do have Western Blot testing available to us that we can use on those types of autolyzed samples.

But for that initial cut, if you can't even tell where that's from, we're not even running the test.

CHAIRPERSON PRIOLA: A last question. Dr.

Bailar.

DR. BAILAR: We heard, I think, that the primary goal of the present testing program is to find out if this agent or these agents are present in the U.S. For that purpose, a focus on high risk animals is 100 percent appropriate, but I think that question has been answered, and it's time to go on now to what I see is the second question, which is how much.

And that question cannot be answered without testing animals that are not perceived as being at high risk.

What are the chances of getting in some testing on a stratified sampling plan of animals that appear to be healthy?

DR. FERGUSON: Actually, I would point out that there are ways to extrapolate information from the targeted sampling that we're doing and carry that over to a broader population. So those are different options that we are looking at.

It can be as straightforward as just looking at ratios based on European data and the sampling that they have done, to more complicated models, to evaluate that and to extrapolate information from one subset of the population to the broader population.

So all of that is still under consideration. I would also say that we really at this point, I don't think we've truly answered the question whether we have the disease here or we haven't. That's what we're going through this effort for. We will have pretty solid details hopefully once the time we're done with this to help answer that question.

We have given consideration to some testing of apparently normal animals. That's a difficult decision to make, and it's a real challenge to consider in a surveillance program. You have to look at, okay, what is our goal, what are we trying to do.

We've established our surveillance program in the most efficient, cost effective way to get done what we want to do. We will consider other options depending on available information and the data that we get, but at this point in time, we're still focusing on a targeted high risk population.

CHAIRPERSON PRIOLA: I think we had better move on to the open public hearing section, but you can keep your questions in mind for later.

Bill.

DR. FREAS: As part of the FDA Advisory

Committee process, we hold open public hearings to the members of the public who are not on the agenda who will have an opportunity to express their comments to the committee. These include both written and oral presentations.

At this time I've received three written requests for the public record. They are in your red folders, and I have a cover sheet like this. They're available on the outside table upon request, and they'll also be posted on the Web shortly.

They are from a woman in the U.K. regarding a letter to her husband's consultant on vCJD and questions for this meeting.

The second submission is an E-mail from Terry Singletary, and the third submission is an E-mail from Ms. Sachau.

These letters are for your reading.

We also have five oral requests for presentations at this morning's meeting. These presentations will be limited to a maximum of eight minutes. The presenters are asked to make any statements that they have regarding financial affiliations that they have with any products they wish to comment upon.

The presentations will be limited to eight

minutes. You have an option if you're one of these speakers. You can either advance the slides yourself up here or you can have the AV team advance the slides for you. It's just when you come up to the podium, you have to let us know whether you want to operate your own slides or whether you want to say "next slide," and have somebody advance them for you.

Dr. Priola, would you read the required statement for this meeting?

CHAIRPERSON PRIOLA: Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To insure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include the company's or a group's payment of your

travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. FREAS: Okay. Our first request is from Abbott Laboratories, Dr. Figard will be the presenter.

DR. FIGARD: Good morning. My name is Steve Figard. I am an employee of Abbott Laboratories, and I've been working with Enfer Scientific out of Ireland for the last three or so years, working with them on their assay.

What I wanted to briefly do today is just give you an overview of how the Enfer BSE assay works. The primary focus is on our recent work on automating what we call the front end of the assay, which I'll show in the next slide, and then give you a brief data review from an external evaluation that's been ongoing in Europe at this point in time.

At this point I want to make a brief legal disclaimer. You'll see down there at the bottom it

says "Enfer TSE kit." The kit has only been approved in this country for BSE testing. However, it is used in Europe for scrapie testing as well.

According to my regulatory people I have to make sure that you understand that it's only used for BSE testing in this country.

Okay. You can break down the Enfer assay into four general areas. The first is sample preparation in which the tissue, brain stem tissue is cut. It gets put into an homogenization buffer and is homogenized, and then that is clarified to some extent by a centrifugation on a plate.

The supernatant from that centrifugation gets transferred to a different test plate. These are 96 well ELISA plates where the sample simultaneously is digested by PK so that any normal prion is removed, and then the protease resistant PrPsc get absorbed nonspecifically to the polystyrene of the plate.

The plate then is washed with salt. It is treated with guanidine HCl and sodium hydroxide, and this opens up the protein to allow greater access for the antibody to subsequently come in and bind.

The immune reactions then include your standard ELISA plate reactions with a primary polyclonal anti-PrP rabbit antibody. With the

appropriate washes in between, you then come in with a secondary HRP labeled goat anti-rabbit IgG.

Then again, with the appropriate washing you add your substrate and read signal, and the signal is a chemiluminescence signal.

Now, what we mean by front end automation is we've addressed some of the more labor intensive or difficult portions of the assay at the front end of the assay, so to speak, during the sample preparation and the initial sample treatment.

The first thing we've done is I'll show you in the next slide how we do the cutting, but we've developed a new, safer cutting tool. We've got a new automated instrument that does homogenization much faster. We've replaced a bag with a tube that makes sample handling much easier. We've streamlined the sample process and, as I'll show, we still have the same performance as we had before.

This is how it's currently done, and this slide gives me the heebie-geebies every time I see it because it's obviously stages. The person that is wearing these gloves doesn't even have the appropriate safety gloves underneath. I assume you that in the lab both at Enfer and whenever I'm doing it in the R&D lab, I've got the appropriate safety gloves under

there.

But we do use a razor blade, and what we have developed is this plastic punch that works a whole lot better and certainly a lot safer, and you simply place the punch on top of the tissue, rotate it back and forth down through and you basically create a small plug that can then be put into the tube.

By using or introducing this, we will be eliminating sharps. It's a lot easier for disposal. The cuts are much more standardized in size and weight. It's just as rapid and inexpensive as a razor blade.

Now, the plastic bag that the sample is normally put in now in the manual assay is this bag, and there's this plastic mesh screen in the middle, and you put the sample on one side, add your solubilization buffer, and I'll show you in the next slide the stomacher that's used, but this bag is a little bit tricky to deal with and requires a certain amount of manual dexterity.

The new automated instrument uses this tube, and the sample is simply dumped into this outer tube, and then this grinding shaft is placed inside the tube. The grinding shaft at the bottom here has a surface that will grind the material to help

solubilize it. There are slits at the bottom here that allows the solubilization buffer with the solubilized material to go up into the center part, and then in the automated system the fluid is withdrawn through the top of the shaft in the middle there.

Before working on this assay, I had never heard of the stomacher, and all this is is a machine that's apparently used in the food processing industry fairly well, and it has got two paddles that you can't see very well, but they're right in there, and they just bounce back and forth and wallop this solution into subjection, so to speak.

(Laughter.)

DR. FIGARD: And you can get two bags into one stomacher at a time, and it actually works fairly well, especially with soft tissue like brain tissue.

We're replacing that with what we're calling an Enfer tissue disrupter system, and of course, as scientists we can't get away without our acronyms. So that's EDTS.

This will process eight samples in ten seconds. The individual tubes get placed in the rack. They're set in there. You press two buttons. The shafts come down, rotates the shaft in the tube very

quickly, and you get your solubilization of your tissue.

As compared to the stomacher, you can do two bags at a time. Each are stomached for two minutes. So to get the same age samples takes four minutes. So there's a significant saving in times with this.

You streamline the sample process in that once you put the sample in the tube, you just basically play with the tube. You add your solubilization buffer in the rack. You can then put it into the EDTS, and then our final component of the automation includes this instrument, the Tecan that we use to do automated sample pipe heading from the EDTS tube to the centrifuge plate, and then after the centrifugation from the centrifugation plate to the test plate.

We also use it to automate the addition of the Enfer Buffer 2, which is our Proteinase K to the test plate, and it will take about five minutes for one plate of 44 samples.

The EDTS rack fits -- those eight tubes goes directly from the EDTS right over to the Tecan and fits right in there. So there's no problem with that.

We have other standard features of automation.

LGC is a lab in the U.K. that has done some of the specificity testing for us. They had 6,894 confirmed negatives. We do test in duplicate. We're dealing with an antigen that is very difficult to solubilize. So getting a truly homogeneous suspension is not guaranteed.

In this first we had six what we call initial reactives that were plus-minus. The rest were negative. Retesting, which is the standard protocol, those six were double negatives, and so we had 100 percent specificity here.

In a separate lab we had 200 positive samples from the over 30 month population; 200 negative samples that were fallen stock and were described as severely autolyzed.

Autolyzed samples, one of the main problems there is you can have levels of protease inhibitors and any assay that depends upon a Proteinase K is going to have the possibility of false positives. So autolyzed samples in a negative population are very important to evaluate this.

The results are shown in this slide. All of the negatives were negative down here. All of the

positives were positive. So in this particular set of samples we, again, had 100 percent sensitivity and specificity, including the fact that we're having worst case negatives in the sample, in the autolyzed.

If there's time for questions, I'll be happy to address the questions.

DR. FREAS: Unfortunately we have to move along right now and we may have questions if time permits at the end of the open public hearing.

Our next requester is from Adlyfe, Incorporation. The presenter is Dr. Alan Rudolph.

DR. RUDOLPH: Thank you very much. thanks to the committee for the opportunity to speak.

Adlyfe is a new company in Rockville, Maryland. We were started by a contract from DARPA, and we have funding from NIH as well, and we're dedicated to diagnostic products for neurodegenerative diseases, and I am currently the CEO of that company.

With regard to diagnostics for prion diseases, we have to recognize that the aggregate nature of this protein represents some fundamental challenges in detection of the material. These challenges are represented both in the detection itself, as well as sample preparation for a high hydrophobic as well as sometimes aggregated protein

from different materials.

We have developed a novel set of ligands which mirror the folding process in which we're directly measuring misfolded PRP so that we don't have any Proteinase K treatment, and we can directly look for the disease in a variety of samples.

We're developing a kit and what we'll show you is the ability to detect misfolded PrP and blood sample from positive BSE animals, which we recently tested in the U.K.

We've also done control challenge studies in hamsters and shown ante-mortem presymptomatic detection of PrP misfolded protein in both braining tissue and in blood samples.

The final two bullets on this slide talk about some of the issues for the field of detection in general and our experiences over the year of our lifetime in trying to move our product forward to the market. The lack of controlled studies and matched samples to correlate the etiology of disease from risk materials in these animals over the expected time course of disease, which is relatively long, limits progress in new diagnostics that may be ante-mortem, more sensitive, and able to detect in blood materials.

The standardization of source materials is

desperately needed to provide accelerating testing, accelerated development of needed tests.

The principle we're operating on is a rather unique principle in which we can look at the direct misfolding of PrP as it goes from a largely alpha-helical confirmation to a folded beta-sheet confirmation, and then subsequent aggregations of beta sheet, the typical types of plaques that we see upon histological sections.

We've created new ligands for sequence matched to regions of the protein that undergo folding that have been tagged with fluorescent labels that are sensitive to the position of those labels as a result of the folding of ligands. So these small ligands associate directly with PrP misfolded protein, fold themselves, transducing a signal associated with the direct detection of misfolded PrP.

The sensitivity of the reaction comes through an amplification step. The amplification step is generated by these small ligands essentially nucleating other ligands in the solution to also fold, amplifying the signal dramatically and giving us what I show you is sensitive detection, enough to be able to detect it in blood plasma from BSE positive animals.

That's simply read as a fluorescent shift as our ligands go from an open alpha-helical conformer to a closed beta-sheet conformer in the presence of PrPsc. That shift is measured in a diagnostic kit, 96-well plate, and can be measured in standard diagnostic laboratory instruments available in diagnostic laboratories.

This is the data that we collected this summer at the VLA in Weybridge in U.K., with Danny Matthews. On the left in red are BSE plasma samples from matched positive brain tissue that was 30 month and older animals collected at the VLA, positive by Western Blot in brain, and you're looking at the ratio of the fluorescence associated with our test showing positive detection in BSE plasma.

In blue are animals that were suspect negative, Western Blot negative and by our test also negative by BSE plasma with two notable exceptions. In pink on either side of the blue areas are two samples that we were given that were Western Blot negative, but came up positive in the Adlyfe test. We then we back to the VLA, asked them to rerun the Westerns, and they were, in fact, confirmed positive by a rerun of a Western.

So the only two false positives we've seen

in our testing were then reconfirmed as real positives.

We've had considerable experience with animal testing in a variety of animals under a variety of modes of infection. We've done a number of hamster studies in which we've inoculated directly intercranially to create disease. We have PrPsc directly in those animals at three weeks, where typical ELISAs take nine weeks for detection, showing that we can detect early pre-symptomatic in brain, and we have seen blood plasma in those animals at five to six weeks positive for PrPsc.

We've also done an oral gavage which mimics more closely the route of infectivity thought to be taking place in these animals, and we have also seen similar results in an oral gavage study in the ten-week hamster model.

We have also done sheep scrapies in endemic populations of sheep both from the Pullman herd, USDA, as well as the Ames, Ohio herd. In one case of that testing we did get confirmation by the third eyelid test. These were symptomatic animals, and in the other case we were looking at live, on-the-hoof sheet plasmas and showing positive detection in sheep plasma.

And then most recently expanding our testing in bovines. So we're up to about 190, 200 infected animals that we've looked at, and about 100 control animals, and we're considerably expanding our testing.

With regards to threshold of detection, we believe we're in the fentomolar range. There's considerable historical and published data on what kinds of levels one might expect in blood, and using that, we believe we're in the fentomolar range for detection, and it has been pointed out here already that the conventional diagnostics using antibodies, first, don't distinguish between native and PrP misfolded protein, therefore probably underestimating infective doses, and usually operate in the picomolar range. Thus, they're only applied to late stage disease in tissue samples for late stage animals.

We believe based on our testing that our testing is at least a couple of orders of magnitude more sensitive than the current ELISA test enabling the sensitivity for detection of blood plasma.

We're developing a kit that's a high throughput diagnostic kit. These are sequence specific ligands. They're not producing antibodies. They can be produced synthetically, and therefore, the

costs can be dramatically reduced and large scale production of components of the test, and we are producing kits for validation and starting to work with the appropriate agencies to look for validation and regulation of our test both in the United States and in Europe.

So in summary, what I've shown in the eight-minute slot that I had was a more sensitive detection to PrPsc that could enable a greater surveillance of risk materials, reducing the risk of transmission of disease, certainly a major concern in a blood supply.

We can detect directly misfolded PrPc in risk materials. We have mostly looked at central nervous system, brain, cortical areas. We have also looked at blood. We have not looked as much into the spleen. We have those samples, and we'll begin to analyze those as well, and those could be good sources for early detection.

We're in discussion with a number of strategic partners to move forward on both diagnostic applications, as well removal applications or other detection such as in surgical instruments, and we'll certainly exploit this unique ligand that we have created to directly detect the misfolding of proteins

in neurodegenerative diseases.

Thank you very much for your attention.

DR. FREAS: Thank you for your presentation.

The next request we have is from Altegen, Incorporated, and it will be a presentation presented by Dr. Bergmann and Dr. Preddie.

This is Dr. Bergmann.

DR. BERGMANN: Good morning. I will tell you about a new test and the background of the test for the detection of human exposure to BSE in serum.

The prion protein transcriptional unit contains two messenger RNA species. One translates the constitutive PrP; the other, a small protein we call prionin. Prionins are usually not expressed in normal subjects, but the prionin gene can be induced in the TSE specific manner.

Prionin genes are present in all mammals investigated so far. Prionin have species-specific, unique antigenic epitopes. Pure synthetic bovine prionin converts human native PrP in a cross-species manner and recombinant PRP to conformers with a 27 to 29 kilodalton Proteinase K resistant core under physiological condition within minutes of contact in the test tube.

(Pause in proceedings.)

DR. BERGMANN: Sorry. The animation is gone in this slide. Thank you.

The gel, the upper gel in the panel shows the product obtained with human PrP after five, 15, and 25 minutes. The lower gel, the left one shows again products with human PrP after 30 and 90 minutes. The lower right panel shows the products obtained with recombinant PrP. This is commercially full size recombinant PrP after 30 minutes, and they are crossed right link.

We suggest that prion proteins are the illusive converting factor in TSE called Protein X and add that prionins play a role in TSE initiation. The model which follows shows how prionins provide means for the detection of human exposure to TSE.

Prionins once expressed are immune modulated. They are treated as an auto-antigen. The anti-prionin IgG in serum can be easily detected with a specific antibody trap ELISA. The immune response declines with time and in some cases prionins escaping the immune control react with PrP cellular form and converts it to PrPsc in a complex.

In this complex prionins are chaperoned to the brain where at the neuronal membranes the complex

dissociates. PrPsc is deposited externally and the prionin enters neuronal membranes and initiates neural degeneration.

Prionins entering -- this unfortunately didn't transmit correctly. I'm sorry -- prionins entering a subject from an external source in the vCJD case of the bovine prionin entering a human are again immune modulated. After decline of immune regulation, again, the prionin can escape and induce the host, the human prionin gene. The human prionin once expressed again is immune modulated as described before.

Those prionins escaping the immune control react with host prion protein to form complex species and different disease pathologies. Most importantly, the subject has two different antibodies with distinct specificities, one for the bovine prionin, the other for the human prionin.

These two antibodies can be detected with the anti-prionin ELISA, and in a cross-species way distinguish between the two if the infection comes from a cross-species way distinguish between the two if the infection comes from a cross-species.

This is shown by data obtained with zero from a suspected vCJD patient. Five months after the first diagnosis of the disease, the serum contained

anti-BSS, anti-bovine prionin antibody, not later on.

The antibody against the human prionin was present throughout the observation period of 20 months in declining fashion.

Blood from donors was tested for the presence of anti-bovine prionin antibody. In samples obtained in Country 1 in the year 2003, all samples were negative for the antibody. Samples obtained from Country 2 in the years 1996 to 1998 collected, in those samples four were positive out of 571. Actually Country 2 is the same country the vCJD patient came from.

This shows that the tests can detect contamination with BSE related bovine material.

Conclusion: prionins are TSE related proteins. Transmitted prionins elicit an immune response. This immune response can be detected with an anti-prionin ELISA.

Endogenous prionins are related to TSE initiation. They elicit an autoimmune response, and this autoimmune response can be detected by the anti-prionin ELISA. Again, the ELISA can distinguish between these immune responses if there is a cross-species contamination.

We suggest that the anti-prionin ELISA

should be used routinely and be added to the array of tests already in use to test blood donations to increase the safety.

Thank you.

DR. FREAS: Thank you.

Our next request is from IDEXX, Incorporation, and the presenter will be Dr. Tonelli.

DR. TONELLI: Thank you.

I am, of course, an employee of IDEXX Laboratories.

What I'd like to do today is bring you through IDEXX's diagnostic, post mortem test for BSE. I'd like to point out that this is truly a second generation post mortem test for prions, and that it detects prions directly and does not require a Proteinase K step.

We are USDA approved, and we have successfully completed the 2004 European validation studies and are in the final stages of approval in Europe. At this point with the samples that we've looked at, we've seen both 100 percent sensitivity and specificity. The advantage of this test is certain in that it's much easier to use in all of the up front sample preparations, centrifugations, Proteinase K steps are removed. It's simply to generate a

homogenate and put it into the ELISA test.

We can combine speed and performance with the ease of use as well.

The key to this is a polymer. We use a chemical polymer to capture the rogue protein PrPsc in the presence of normal PrPc from a simple tissue in water homogenate. Again it removes all of the Proteinase K steps, the centrifugation steps and so forth. It really allows for a much easier automation as you can imagine.

Now, the basis of this is really you can see it's a Seprion technology, but it's all around the use of polyionic and ionic compounds to capture the rogue protein. As you know, there's quite a bit of history of polyanions binding the prions, and what we've been able to do with our partners is to develop conditions where we can specifically capture PrPsc in the presence of PrPc. The detection occurs with an anti-prion antibody.

So this is the application. We have this ligand for binding, and some examples of the types of binding could be the types of polymers that work in the situation, a pentosan sulphate and detran sulphate, et cetera.

We do use some matrix busters. We use

trypsin and DNAse just simply to break down the viscosity of the sample. It does not digest PrPsc, and you can see that clearly on Western Blots.

And then there are surfactants to enhance and allow this binding to occur.

This just simply shows the overall protocol, but again, it's very simple in terms you generate the homogenate by whatever method you like. The method that we have approved in the U.S. is a bead beating method that's used in other methods as well, and you can take the sample as you wish. You can dissect it out. You can take it with a syringe. You can get your sample however you wish, and then homogenize it, and then it simply goes into a microtiter plate, is diluted and run in a typical ELISA.

On the ELISA automation, we use a commercially available tecan Evo automation platform. It's very simple. In fact, it's even simpler than it performs here. There's no incubators. There's no heating or cooling steps. It's simply liquid handling and liquid addition, and our current protocol, we can do nine plates of samples in just under five hours, which is almost double, I think, throughput of most other assays that are out there.

This is what information we can show you at this point from our EU studies and samples as well that we've run in other parts of the world, and there's a negative distribution of the population and our cutoff, and you can see that we are quite a way from, quite a number of standard deviations away from the cutoff population, which indicates that we should see and have seen excellent specificity.

And think there are 14,000 or so samples in this assay, and these are samples that come from a variety of sources. They're normal slaughter samples. They're downer animals. They're autolyzed samples, just a whole variety of samples that are in that negative population.

The Phase 1 European trials where we run 150 negatives and 50 positives. Again, I think all of the tests had to run through this first, and we got, of course, 100 percent agreement there.

This is just to show you the agreement with another EU approved test with the IHC positive samples. You can see overall there's pretty good agreement between the two tests. Remember you need to meet an IHC. IHC is the gold standard, and so you have to meet that as the standard of positivity.

This is just simply a dilution series

against a positive sample in the negative brain against an EU approved test to show equivalent sensitivity in this application.

And this is just to give you some idea of autolyzed samples. These are normal samples that were just held to 37 degrees and run over a period of days, and you can see they are negative samples, and they stay negative.

We have positive samples as well, and the positives stay well. In fact, in some cases they get a little more positive. I think that's because the viscosity of the sample is being reduced over that period of time.

So in summary, we'd just like to give you an idea that the test does have strong performance. We have see no false positives in the 15,000 or so samples we've run so far in that sample set. We have 100 percent correlation with the European approved product. We have USDA approval, and we've successfully completed the 2004 EU validation studies.

The benefits of this, I think, are a couple. One, it's easy to use. It's fast and efficient, a lot less hands on time, and no extra equipment. We don't have to automate any of the front end stages. It's simply automating the assay itself.

Because there's no PK step, there's really less chance for error. You don't have to worry about the PK. Youdon't have to worry about the conditions and so forth, and there is an automated platform.

Thank you.

DR. FREAS: Thank you.

The next request is from Microsens Biotechnology.

DR. WILSON: Thank you for allowing me to speak.

I just wanted to tell you about our progress towards a feasible blood test for TSEs and present you with some recent data.

In line with a lot of people these days we don't like this Proteinase K step. We don't like it because there's no guarantee that all of the rogue prion (phonetic) is proteinase resistant. This is becoming reported now with atypical scrapie and BSE, which has got implications for food safety, but also when we started this work, we didn't know what state the rogue prion in blood was likely to be, whether it's likely to be resistant to Proteinase K or not.

So Quentin Tonelli from IDEXX has already described the Seprion ligand use in post mortem field and has told you that it's a polyionic polymer that

can specifically capture the rogue prion protein and avoid the need for Proteinase K.

So this polymer does have a pedigree in the post mortem field.

Just a couple of slides showing proof of principle really. This work was carried out by a group at the Veterinary Laboratories Agency in the U.K., Roy Jackman's group, and it simply showed that if you take the Seprion and coat it onto magnetic beads and interrogate BSE infected and uninfected brain samples, you can elute the captured material, run it on a Western Blot, and plate it with an anti-prion antibody. You only get prion material in the infected brain.

So this ligand really does only bind. Of course, there's no protease involved here, no Proteinase K. So it really does bind specifically to rogue prion without the use of Protinease K, but the material that is captured is protease resistant, as you would expect in that if you pretreat the brain with Proteinase K before capture or treat the captured material after capture, the signal doesn't decrease, but you get a lopping off of a bit of the protein. So the mobility does increase.

Okay. So that's all I wanted to say aobut

the ligand and its pedigree.

What has surprised us when we've been looking at blood perhaps is that there's an awful lot of rogue prion in blood, but the rogue prion in blood in our experience isn't the same as the prion that we find in brain.

So we spent a bit of time doing spiking studies and came to the conclusion that these really aren't adequate to mimic the blood borne infection, and in fact, we've only made significant inroads into detecting blood borne prion when we actually achieved some animal models, scrapie models.

I've presented this slide before, and it shows our results when we were investigating scrapie infected and uninfected sheep, and there's not many results in this slide because these samples are as valuable as hen's teeth, and at that time we had five infected animals and a few controls. This just shows one day's experiment really, looking at five infected animals and the two controls.

At that time we were looking in five mLs of blood, looking at the non-red cell fraction, and you can see clearly distinguishing a signal from the scrapie infected animals.

The labels always drop off this slide.

I'm not quite sure why, but this set of animals here is from an exposed flock, and you can see that we get a range of signals scrapie exposed animals. These are asymptomatic animals that six months later went on to pretty much all of them developed clinical disease.

We've got a set of controls here from unexposed New Zealand derived animals, and you can see clearly that the negative animals give very low signals compared to some of the asymptomatic animals.

Again, that's using five to ten mLs of blood.

We went on to use the same assay on some human samples. We were lucky enough to get some suspected iatrogenic CJD patient and a suspected vCJD patient. We already knew that the assay -- of course, you could work on post mortem sporadic CJD and vCJD samples, and it worked on vCJD spleen, and we could use it to spike the spleen into the plasma. As I said, we don't like those spiking studies at all.

When they put the panel of samples through the assay with a load of control samples, the only sample that came up positive in the assay was from the suspected iatrogenic CJD patient. Tragically that patient has gone on to develop full-blown disease.

The vCJD suspect did actually recover, so

obviously wasn't a vCJD infection at all.

Now, I know that me standing up and telling you what we can do is not very convincing unless we can have some sort of independent evaluation, and the way we tried to do that is to work on a blind panel. We requested a blind panel of scrapie infected and uninfected bovine blood from the VLA archive. We received those samples in August 2004.

Unfortunately the samples were frozen. They came as frozen blood. So we had to develop new protocols to be able to handle that frozen material.

We ran some of the samples through our test and broke the codes. The protocol was fairly simple really. There's a bit of front end treatment, lyse the blood, DNAse-treated. There's a black box step there that I can't say too much about at the moment in time, and then capture on Seprion-coated magnetic beads. The beads are washed and then the captured material is eluted and put through an in-house ELISA.

And these were the results once the codes were broken. Now, what these results show is that our assay actually works. We've got quite a good sensitivity, missed one Western Blot positive sample.

Our specificity is letting us down a bit for false positives, at least not picked up by the Western Blot. True, those were from New Zealand derived animals that you wouldn't expect to find positive. Two were from clinical suspects.

This animal here is a clinical suspect, but hasn't yet been confirmed by Western Blot. So if that animal turns out to be positive, we would have these results for sensitivity, specificity, positive predictive value and negative predictive value. If it turns out to be negative the results would be like this.

So once we knew that the assay was working, we could go back to those samples now and put them back through the assay, through a revised protocol. I don't know if I mentioned it. If I did mention it, I'll mention it again. Here we're only using 125 microliters of blood, whole blood, frozen blood, and you can see that once we've revised the protocol we're getting much better results.

We've managed to remove three of the false positives. We have one false positive left which is from a suspected animal. It was clinically suspected to have disease. It wasn't confirmed by Western Blotting. We need to go back and now look at the

brain of that animal, and we have now picked up the animal that we missed that was actually confirmed to be positive.

So we've improved the assay significantly in the short amount of time that we've been working on it.

This is just for your interest. It just shows you some repeats of what we now know to be blood from a positive animal and two negative controls. You can see that if we repeat the assay on three consecutive days, we do get very similar assay signals. So it's a very reproducible assay.

So in summary, we've used the Seprion ligand technology which has the post mortem pedigree to detect PrPsc in sheep with scrapie and in preclinical animals, and we've been able to use the assay to identify an iatrogenic CJD patient.

Now, when we did this work, it was with large volumes of blood, and since then we've been able to adapt the assay to use smaller volumes of blood, which of course is going to be more feasible as a blood screening tool, and at the moment we're investigating a second blind panel with our revised protocol, and we'll decode those results in the near future.

Thank you.

DR. FREAS: Thank you.

Is Jean Halloran from Consumer Policy Institute in the audience?

(No response.)

DR. FREAS: Okay. Her comments if she is not here will be in the afternoon open public hearing. There will be another open public hearing in the afternoon.

Is there anyone else in the audience at this time who would like to address the committee? Please state your name.

MR. CAVENAUGH: Thank you very much.

My name is Dave Cavenaugh. I'm on the government relations staff of the Committee of Ten Thousand, an organization of people with Hemophilia who have contracted HIV and hepatitis from the blood supply and is very much concerned about this entity we have.

This morning's agenda was devoted to the science of the testing of cattle for BSE and this afternoon's will be on the science of clearing of plasma. I can only suggest of the many things that I've seen about the process from the patient view, from the testimony that has been given, the first

piece of the three written testimonies is from the wife of a person with hemophilia, HIV, Hepatitis C, and presumptive CJD.

And I strongly recommend it to you. It poses several questions for this panel specifically about the safety of the U.S. blood supply.

My question to you to please consider as you go through the day is how does the disease get from the cattle being sought for testing to the humans donating blood. I don't mean scientifically. I mean what are the processes.

The third piece of written testimony, the last two pages of it are statements made in testimony by the man who shot the cow in Washington State, and it just opens up -- I'm sure you've all read it by now in some capacity or another -- the questions about the rigor of the decision about what gets tested and what doesn't, the relationship between the USDA agent and the staff of the slaughterhouse, the kind of slaughterhouses that have this experience and don't, and the variation that is reality in life.

You have a U.S. cabinet department now searching for a goal of 20,000 per year tests of only one small subcategory of the U.S. cattle supply, if you will, of 33 million head a year. In the face of

the fact that there are over ten known strains of scrapie, that there is TSE across six different species of animals in the face of the fact that we do not know how the disease gets to humans in the sense of how the cases in England that have been deemed to be vCJD, clinically, scientifically it has not been proven that they got it from beef or how they got it from beef.

You know, we have to proceed without an answer to that. We have to say presumptively, okay, it's diet related, and now because of the two publications last December and this summer it's possibly very likely blood related even though we've had years of evidence that nothing happened.

Our organization has for years talked about but we have Rohwer's rat, which is in a study some years ago by Robert Rohwer here methods of transmission, including intracranial injection, but also vein-to-vein transfusion in 22 hamsters, in the latter one did transmit venously, and you know, we can't say it's not in the blood.

Now, the first person writing the testimony from the U.K. talks about people who have come to this country from England after the ban on European travel and donated blood freely, not getting

screened. How are we looking at how potential incubators are kept from donating to the blood supply?

The case that she speaks of was a man who was exposed to contaminated plasma in 1996, eight years ago. Now he has some symptoms. We know that there's an incubation period issue with this disease. We must be prepared to work in the unknown.

Perhaps the first and clearest step would be set aside some 30 percent of those USDA cattle to be drawn at random, as was discussed briefly this morning so that we have a better screen. We're still testing only one percent of our cattle at present, and they're gearing up. That's wonderful. They only tested 2,000 per year before, and that was the most recent year before the current effort.

So I just ask you to keep your eyes on the fog. There are unknowns here at the front end of the cattle testing process, in the middle of the cattle-to-human and in the human donation process, in addition to the cleaning, clearing of the plasma.

Thank you very much.

DR. FREAS: Thank you.

Is there anyone else in the audience who would like to address the committee at this time? Dr. Epstein from CBER.

DR. EPSTEIN: Yes. Thank you very much.

I just wanted to clarify. Mr. Cavenaugh, you seem to be suggesting that there's a potential case of vCJD in a hemophiliac treated in the U.K., but we have conferred with U.K. authorities, and to our knowledge there is no such case.

That's not to say that there are no neurological diseases in hemophiliacs in the U.K., but obviously this is an alarming statement. The entire world, certainly the U.K., and certainly the U.S. are very attentive to monitoring for that possibility, but I think it's very important to have a clear record that at least at this point in time there is no presumptive case of vCJD in a patient treated for hemophilia, and Dr. Will, perhaps you would corroborate that statement on my part.

DR. FREAS: A quick comment.

MR. CAVENAUGH: There was some reason for the U.K. Department of Health to transmit letters to 6,000 people with hemophilia that they were at the highest risk for CJD and to their physicians indicating the commencement of several different procedure changes, such as bans on sperm donation, on requirements of non-reuse of surgical instruments.

If we don't have a diagnosis because the

man is still alive, thank God. If we have symptoms that have been seen in a compendium of 27 cases of vCJD of the 143 that have died, that match in the eyes of this nurse and residents, it's worth looking at. Caution is what I'm urging.

DR. FREAS: Dr. Epstein.

DR. EPSTEIN: Okay. Well, I think that's a helpful clarification. We are aware of the risk assessment that was done in the United Kingdom on certain products and the fact that those product recipients have been notified. It remains the fact that there are no products licensed in the U.S. made from U.K. plasma.

Additionally, there are no products that have ever been distributed in the U.S. from which there was a product made including plasma from a person who later developed vCJD.

We do hope, however, to review the U.K. risk assessment. We are engaged in a preliminary risk assessment of U.S. products made from U.S. plasma. Preliminary results do suggest that the risk of the U.S. products is significantly less than the estimated risk of U.K. products, and we do expect to present a more complete discussion and review of that issue at the next TSEAC meeting in February 2005.

So I think your comments about the need for careful watching are well placed, and we do share that perspective.

DR. FREAS: Thank you.

There will be another open public hearing in the afternoon. At this time we're going to close the morning's open public hearing and get on with the meeting.

CHAIRPERSON PRIOLA: Okay. Our next speaker is going to present some -- it's another informational topic. Dr. Scott.

DR. SCOTT: Good morning. This presentation follows on from a February 2003 meeting of this committee where you discussed, we discussed labeling claims for TSE clearance in plasma derivatives.

The committee voted at that time that the FDA should consider evaluating submissions from industry concerning TSE clearance, and that these studies from industry could support a description of those same studies in labeling.

So what I'm going to do is give you some of the background that you've already had but not in as exhaustive a detail as you saw at the February 2003 meeting, more concerning the rationale and how we went