U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE

17th MEETING

TUESDAY,
FEBRUARY 8, 2005

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

PRESENT:

SUZETTE A. PRIOLA, Ph.D.,	Chairperson
JAMES R. ALLEN, M.D.	Temporary Voting Member
ERMIAS D. BELAY, M.D.	Temporary Voting 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.	Temporary Voting Member
DONNA M. DiMICHELE, M.D.	Temporary Voting Member
PIERLUIGI GAMBETTI, M.D.	Temporary Voting Member
DAVID W. GAYLOR, Ph.D.	Temporary Voting Member
R. NICK HOGAN, M.D., Ph.D.	Member
ALLEN L. JENNY, D.V.M.	Member
RICHARD T. JOHNSON, M.D.	Member
FLORENCE J. KRANITZ	Consumer Rep
GEORGE J. NEMO, Ph.D.	Temporary Voting Member
STEPHEN R. PETTEWAY, Jr., Ph.D.	Acting Non-Voting Industry Rep
MO D. SALMAN, Ph.D.	Member
LAWRENCE B. SCHONBERGER, M.D.	Temporary Voting Member
GLENN C. TELLING, Ph.D.	Member
WILLIAM FREAS, Ph.D.	Executive Secretary

FDA REPRESENTATIVES:

STEVEN ANDERSON, Ph.D., MPP
JAY S. EPSTEIN, M.D.
PEDRO PICCARDO, M.D.
DOROTHY SCOTT, M.D.
MARK WEINSTEIN, Ph.D.
ALAN E. WILLIAMS, Ph.D.

INVITED SPEAKERS:

SHEILA M. BIRD, MA, Ph.D.	Cambridge University
LISA A. FERGUSON, D.V.M.	USDA
ANNA M. MOLESWORTH, BAHons, Msc	U.K. Health Protection Agency
LYNNE SEHULSTER, Ph.D., M(ASCP)	Centers for Disease Control and Prev
KATE SOLDAN, Ph.D.	U.K. Health Protection Agency

A-G-E-N-D-A

AGENDA - (Continued):

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

8:06 a.m.

EXECUTIVE SECRETARY FREAS: Mr. Chairperson, Members of the Committee, invited guests, and members of the public, I would like to welcome all of you to this, our 17th Meeting of the Transmissible Spongiform Encephalopathies Advisory Committee. I am Bill Freas, the Executive Secretary for today's meeting.

The entire meeting today will be open to the public.

At this time, I would like to go around the table and introduce the public to the members seated at the table. We will start on the right-hand side of the room. Would the members please raise their hand as their name is called, so people can see who is who?

In the first chair is Doctor Larry Schonberger, Assistant Director for Medical Science, Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention.

Next, Doctor Nick Hogan, Assistant Professor of Ophthalmology, University of Texas Southwestern Medical School.

Next, Doctor Arthur Bracey, Associate

Chief, Pathology, of St. Luke's Hospital, Houston, Texas.

Next is Doctor Allen Jenny, Pathologist, National Veterinary Services Laboratory, U.S. Department of Agriculture.

Next, Doctor David Gaylor, President, Gaylor Associates, Eureka Spring, Arkansas.

Next, Doctor George Nemo, Chief, Blood Resources Section, Division of Blood Diseases and Resources, National Heart, Lung and Blood Institute.

Next, Doctor Richard Johnson, Professor of Neurology, Johns Hopkins University.

Next, Mrs. Florence Kranitz, President of the CJD Foundation, Akron, Ohio.

Around the corner of the table is Doctor James Allen. Doctor Allen is Chair of FDA's Blood Products Advisory Committee, and he's also President and CEO of the American Social Health Association.

Next is the Chairperson of this Committee, Doctor Suzette Priola. Doctor Priola's term was extended for one year so she could continue to serve as a leader of this committee, and we thank you very much for that willingness to do so. Doctor Priola is also an Investigator, Laboratory of Persistent and Viral Diseases, Rocky Mountain Laboratories.

Next is Doctor Glenn Telling, Associate Professor, Department of Microbiology, Immunology, and Molecular Genetics, University of Kentucky.

Around the corner of the table is Mr. Val Bias, Co-Chairman of the Blood Safety Working Group, National Hemophilia Foundation, Oakland, California.

Next is Doctor Lynn Creekmore, Staff Veterinarian, APHIS Veterinary Services, U.S. Department of Agriculture.

Next is Doctor Stephen DeArmond, Professor, Department of Pathology, University of California, San Francisco.

Next is Doctor Ermias Belay, Medical Epidemiologist, Division of Viral and Rickettsial Diseases, Centers for Disease Control.

Next is Doctor Mo Salman, Professor and Director, Animal Population Health Institute, College of Veterinary Medicine and Biomedical Sciences, Colorado State University.

In the empty chair we will soon - it will soon be occupied by Doctor Donna DiMichele, Associate Professor of Clinical Pediatrics, the Weill Medical College and Graduate School of Cornell University.

Next is Doctor Pierluigi Gambetti, Professor and Director, Division of Neuropathology,

Case Western Reserve University.

At the end of the table is our Acting, Non-Voting Industry Representative, Doctor Stephen Petteway, Director of Pathogen Safety and Research, Bayer Corporation.

Doctor DiMichele, you are just in time.

On a solemn note, I do have an announcement to make about a dear friend of this Committee. She wasn't just one of our friends, she was a former TSEAC member and a prominent researcher. Doctor Beth Williams, who served on this committee from January, 1999 to January, 2003, along with her husband, Tom Thorne, died in a tragic automobile accident on Wednesday, December 29, 2004.

At this time, I would like to ask that we take a moment of silence to honor the contributions that Doctor Elizabeth Williams made to us here at FDA, to the contributions she made to the lives of her students at the University of Wyoming, the contributions she made as a wildlife veterinarian through research in the field of chronic wasting disease, and most important, the contributions that she made to everyone she met, whom she treated as her friend. Please join me in a moment of silence.

Next, I would like to read into the public

record the Conflict of Interest Statement for this meeting.

The following announcement is made part of the public record to preclude even the appearance of a conflict of interest at this meeting.

Pursuant to the authority granted under the Committee Charter, the Director of Center for Biologics Evaluation and Research has appointed the following participants as temporary voting members: Doctor James Allen, Doctor Ermias Belay, Doctor Stephen DeArmond, Doctor Donna DiMichele, Doctor Pierluigi Gambetti, Doctor David Gaylor, Doctor George Nemo and Doctor Larry Schonberger.

Based on the agenda, it has been determined that the committee will not be providing advice on specific firms or products at this meeting. 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 and Drug Administration prepared general matters waivers for participants who required a waiver under 18 U.S. Code 208. Because general topics impact on so many entities, it is not

prudent to recite all potential conflicts of interest as they apply to each member. FDA acknowledges that there may be conflicts of interest, but because of the general nature of the discussions before the committee these potential conflicts are mitigated.

We would like to note for the record that Doctor Stephen Petteway is acting as the Non-Voting Industry Representative for this committee, on behalf of regulated industry. Doctor Petteway's appointment is not subject to 18 U.S. Code 208, he is employed with Bayer Healthcare Biological Products, and thus has a financial interest in his employer and other similar firms. In addition, in the interest of fairness, FDA is disclosing that Doctor Petteway is a Scientific Advisor for Hemocellular Incorporated.

With regards to FDA's invited guests, the Agency has determined that the service of these speakers are essential. The following interests are being made to allow meeting participants to objectively evaluate any presentation and/or comments made by these invited speakers. Doctor Sheila Bird is employed by the Medical Research Council in Edinburgh, United Kingdom. Doctor Lisa Ferguson is employed by the USDA Veterinary Services in Hyattsville, Maryland. Ms. Anna Molesworth is employed by the Health

Protection Agency, Centre for Infections and Communicable Disease Surveillance Centre, London, United Kingdom. Doctor Lynne Sehulster is employed by the Centers for Disease Control and Prevention, Atlanta, Georgia. Doctor Kate Soldan is employed by the Health Protection Agency, Communicable Disease Surveillance Centre, London, United Kingdom.

Members and consultants are aware of the need to exclude themselves from discussions involving specific products or firms for which they have not been screened for conflict of interest. Their exclusion will be noted for 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 by written request under the Freedom of Information Act.

So ends the Conflict of Interest Statement for the public record.

Before I turn the microphone over to the Chair, I would like to request if you have a cell phone on, could you please put it on silence, or turn it off. Your neighbors would appreciate it.

Next, I would also like to say that we

always have a timing light to time the speakers to make sure that everything stays on schedule, but, unfortunately, the timing light is in a car, and the car is impounded in a parking lot at this time. If we get the timing light back with the car attached, we will be using it later on in the meeting. However, in the meantime, when your presentation has about two minutes left, I'm going to turn my little red speaker light on, and that will be your warning to think about concluding your presentation in the next couple of minutes.

Doctor Priola, I turn the meeting over to you.

CHAIRPERSON PRIOLA: Thank you, Bill.

First of all, welcome back, everybody, from the last committee and the new members as well. I think if you've gone over the topics we all realize that the first two topics, the questions that are asked are not necessarily voting questions; they are more essay questions, which is going to - could make things very difficult a we go through and discuss matters, but, fortunately, the first two topics, I think, will overlap significantly in many ways.

So the things you want to keep in mind as you hear the presentations is that we've been asked

to, essentially, assess the risk models that the FDA is using for risk of exposure to variant CJD from plasma products, and so we've been asked to comment, essentially, to give these a critical review and to comment on the validity of the models, the sensitivity, are the parameters sufficient, are they varied enough, should we use U.K. survey data as input? Just as examples, these are things that you should keep in mind as you listen to the presentations as we get ready for our discussion.

So, because we have a very full schedule, and because we don't have a timing light, which makes things a little bit tougher, I'd like to get started with our first speaker, who I believe is Doctor Lisa Ferguson, who is going to update us in an informational presentation on BSC surveillance in the U.S.

DOCTOR FERGUSON: Thank you. Good morning, everybody.

My presentation, actually, will probably be pretty quick, because I think most of you all have heard me do this several different times, and just with updates on numbers.

So, I'm primarily going to talk about what we're doing in surveillance in the U.S., but just as

a reminder for everybody as to what's happening worldwide, and to try to make a point, cumulative total, actually, at this point in time, identified cases worldwide are greater than 189,000. The vast majority of those, greater than 96 percent, are still in the U.K. Actually, perhaps, more interestingly, more than 89 percent of those have actually occurred in 1996 and before, so if you look at the curve in the U.K. I think everybody is real familiar with that, where you had a peak in '92-'93, and then a significant drop off, but even if you look at the curves in Europe it also appears to be dropping off again. So, we do appear to know what we are doing, at least in the animal health community and are getting things under control worldwide.

Actually, if you are interested in the numbers, the OIE, the World Organization for Animal Health, does post fully-updated numbers on their website, which is oie.int, and go over on the left under animal health status and they've got a few pages specifically for BSE, with reported cases worldwide.

So, let's talk about what we are doing in the U.S. I think as everybody knows, beginning in June of 2004 we started an enhanced BSE surveillance project, and our goal is to get as many samples as we

can from the targeted high-risk population in a 12 to 18-month period.

We're targeting population where the disease is most likely to be diagnosed, so if it's present, this targeted population, which are adult animals with some type of clinical abnormality that could even remotely be considered consistent with BSE, and this is the most efficient way to help us identify is the disease here, and if so, to help us put some parameters around the possible prevalence level.

We've had lots of questions raised about how we've set up our program and why we are doing it this way, but our assumption was, if we can't find disease in this targeted population, or the most likely place to find it if it's here, then it's even more unlikely to be found in the non-targeted population or the clinically-normal animals.

We can use the data that we collect from the targeted population to extrapolate information to the broader cattle population.

We estimate that our targeted population is about 446,000 animals. It was a bit of a challenge to try to come up with these estimates, but we've used different surveys that we've done to try to estimate animals that die on the farm. We have worked with our

colleagues in Food Safety Inspection Service to get estimates of animals that they condemn on ante mortem inspection, for reasons that would be consistent with our target. This is out of an adult-cut cattle population of 45 million.

So, these are the types of animals that we are looking for, clearly non-ambulatory animals, those animals that are down for some reason, can't get back up, dead stock animals that die for unexplained reasons, field cases of central nervous system signs, on-farm suspects. We are working with veterinary diagnostic labs, if they get these neuro cases, or dead stock, or downers, also working with public health labs as they get rabies suspects that would also fit our target, and last but not least, we are continuing to work with our colleagues in the FSIS that are in slaughter plants, and any animals that are condemned on ante mortem inspection for slaughter are sampled.

Now, just to step back for a minute and look at where we've been in the past, these are total numbers of samples that we've examined previously on a fiscal year basis. You can see our sampling really stepped up in 2002, 2003, with approximately 20,000 samples each year. That last bar of '04, actually is

just the first part, these are fiscal years, which start in October, so this is our fiscal year that started in October, '03 through the end of May, '04. When we started the enhanced program, we stopped collecting, we essentially, made a break in our data and are reporting that out separately.

Just to show you proportions of where that's been in the past. The yellow bar are total samples collected per year. The purple bar are those animals that are non-ambulatory or down, and the blue bar are dead stock, so the vast majority of our samples collected in the past are dead stock and downers. The other remaining ones in there would be CNS cases, other clinical signs that would be consistent with BSE.

So this is where we've gotten to since we started our enhanced program the first part of June. We are up over 221,000 samples so far. Primarily, we are using rapid screening tests, one of the ELISA tests for the initial sampling, many inconclusives then are sent to our National Veterinary Services Lab, where we are using immunohistochemistry as our primary confirmatory test. We are doing some screening, though, still with IHC, about 4,200 of those. So we feel like we are actually on track for where we need

to be about halfway into this project, and we're continuing to analyze the data. We haven't released a lot of the detail publicly, that's still going through some clearances. Hopefully, we'll be able to distribute some of that shortly, because I know people are keenly interested in how we are doing and some breakdowns of that, rather than just raw numbers.

But, we are looking at this routinely, making sure that we're getting appropriate geographic distribution, and that we are getting the populations that we expected. So, geographically, actually, we feel like we are doing very well. The vast majority of our samples are still from non-ambulatory dead stock, clearly as we expected, and we are also getting good representation from all the different collection sites that we are working with.

Just to re-emphasize, for folks that aren't familiar with the industries, primarily, we are working with animal disposal facilities, renderers, 3D/4D salvage slaughter facilities, dead stock haulers, these types of places. So, as expected, that's really where we are getting the vast majority of our samples.

So, we are very encouraged by our results, and by the success that we've had in getting the

samples. We do plan on continuing this, at least for a 12-month period, and we'll see where we are here in a few months.

As we analyze the data, then we'll decide where to go from here. We are already looking at different options for surveillance when we get this project done. No decisions have yet been made. Clearly, a lot of that depends on what we find in the rest of our surveillance effort, what our neighbors to the north find, and how that might impact us.

We do have a lot of information on our website, and here's the website address, click under Hot Issues in BSE, and we update our testing numbers weekly, and also a lot of other detail about how we are going about things can be found on that same website.

So, questions?

CHAIRPERSON PRIOLA: Yes, Doctor Belay?

DOCTOR BELAY: Yes, in one of your slides you had the targeted population of about 400,000. It looks like the captive population was about 200,000. Is that just based upon the fact that the estimate was sort of on the high side, or is there some issue with compliance in the testing?

DOCTOR FERGUSON: Our estimate of the

targeted population is, that's how many animals would show up in that population in a year, so at the end of a year we hope to be fairly closer to that. We are about halfway into this, with more than 221,000, so we think we are - both our estimate was on track, and our numbers are on track.

CHAIRPERSON PRIOLA: Doctor DeArmond?

DOCTOR DeARMOND: Could you explain what the compliance rules are? Is this still voluntary? How are you getting these? How are you encouraging people to give you these samples, and what do they actually send you?

DOCTOR FERGUSON: Okay.

We have a field force throughout the U.S., where we have APHIS employees in every state, and they are working with the various facilities and with on-farm producers to obtain these samples.

The whole question of voluntary versus mandatory does get a bit complicated. At this point in time, these industries are cooperating with us. We've built up a lot of good will with them over the past several years. We recognize that we each need the other, so they've always been very cooperative, and we're building on that.

We do, however, have the authority, in

March of last year we published what we call the Blood and Tissue Collection Docket, where the Department does have the authority in slaughter and rendering facilities to go in and mandate that we take samples for surveillance, not just for BSE, but for any other animal disease.

We have chosen to try to work cooperatively with the industry, first of all, and not go in with a big hammer and make people do things. And, we feel like we're getting very good cooperation.

We did get a significant amount of emergency funding to help us run this program, and we're using that to do cost recovery. Essentially, these guys are incurring additional costs, so we are covering those costs for them. Also, with producers, if they are calling us directly to help encourage that, then we will pick up the cost of disposal of the carcass for them, so it makes it a cost-neutral option for the producer. And, essentially, for the rendering facilities through a D40, if they are doing additional things, specifically for this program, then we are covering those costs for them.

DOCTOR DeARMOND: And, the tissues that you get?

DOCTOR FERGUSON: Oh, sorry, sorry, yeah,

they are collecting, essentially, brain stem, sending those in, fresh tissues. It's either an APHIS person doing the collecting, either a permanent employee, we've hired a bunch of temporary employees also, in some instances we have hired a contractor to do that collection for us, but it is fresh tissue that they are sending in to one of the designated labs. If you are in a given state you send stuff to a designated lab.

DOCTOR DeARMOND: Do they scoop it out from the foramen magnum?

DOCTOR FERGUSON: Yes, yes, the standard scoon -- spoon scoop technique, yes. Sorry. It's too early for me.

CHAIRPERSON PRIOLA: Doctor Gambetti?

DOCTOR GAMBETTI: Can you tell us what are the criteria to declare an animal positive, or a result positive? I see that you run two tests, the ELISA and the immunohistochemistry. What are the criteria to run the two tests, or do you run two tests, the two tests together, or alternatively, and what are the criteria for declare an animal positive? Is it just positive with one criteria or both, or can you tell us about this?

DOCTOR FERGUSON: Yes. I can tell you in

somewhat general terms. If you want to get into specifics about literally how we are doing each of the tests at NVSL I'll call on one of my colleagues on the committee.

But, in general terms, the first screening test is done at one of our network laboratories. We have seven state/federal labs that are working with us, and they are using one of the commercially-available rapid screening tests. They are running that according to manufacturer's instructions, and if they get a reactive - or, above a certain OD reading, in accordance with the manufacturer's instructions, that's deemed to be an inconclusive. They then forward that tissue to NVSL, fresh tissue at this point in time.

NVSL reruns the rapid screening test, concurrently then they are putting that tissue in formalin to fix for IHC, and then they are running IHC according to their standard SOP to do an IHC test.

If for some reason they got that tissue and it was not of adequate quality to do an IHC, then we would use a Western Blot in that instance. Also, if we got an IHC positive, we'd then also do a Western Blot to help us characterize what we might have.

DOCTOR GAMBETTI: And, both have to be

positive, or only one can be positive?

DOCTOR FERGUSON: Okay.

Essentially, we are calling things positive based on the IHC. So, if we got reactions on the rapid screening test, you know, a strong reaction at the network lab, a strong reaction at NVSL, that would still be inconclusive. We are not going to call that positive until we get an IHC positive, and then at that point that would be deemed positive, based on the IHC results.

DOCTOR GAMBETTI: Let's assume the Western Blot is positive, and the IHC is negative, then it will be called negative?

DOCTOR FERGUSON: Well, we are using Western Blot only if we have tissue that is not of sufficient quality to do IHC at this point in time, or if we already have an IHC positive.

CHAIRPERSON PRIOLA: Doctor Hogan?

DOCTOR HOGAN: Yes

My understanding is you are testing animals that are submitted to some facility or rendering plant or something like that. Is there any - what's the percentage, if you can guess, of dead or downers never make it to a facility that aren't even submitted for testing?

DOCTOR FERGUSON: I don't know that you'd ever be able to come up with a percentage. I mean, you know, it's a wild guess to try to say how many animals die on a farm in a given year. We've done different surveys to try to come up with, or used information from general animal health surveys that we've done to try to come up with estimates of that. Whether that's accurate or not, we have no clue.

That 446,000 number that I showed as an estimated high-risk population, probably about 220,000 to 250,000 of those were from that estimated die on the farm. Now, that just means they die on the farm, that doesn't mean they stay there, because we recognize that a lot of producers, they don't want a carcass on their farm, and many of them have environmental issues, they can't bury animals, et cetera, so we recognize that a lot of those are going to the rendering facility, the dead stock guy, the 3D/4D plant, just to get them off a producer's place.

We are, however, looking at the information that we have. We are trying to track, you know, collection sites, whether it's on the farm, whether it's a rendering facility, a 3D/4D, in those states where, based on their local knowledge, our folks say, you know, there's not a rendering facility,

and they are really focusing on getting on-farm collections, they are doing very well.

So, those numbers are looking pretty good. We are getting a good proportion of those.

CHAIRPERSON PRIOLA: Doctor Schonberger.

DOCTOR SCHONBERGER: Lisa, could you remind us, assuming that the targeted surveillance continues and everything is negative, what is the conclusion about the prevalence of BSE in the United States? The sample was selected so you could come to a specific conclusion, is that not true?

DOCTOR FERGUSON: Well, sort of true. And we've had lots of questions, and lots of entertaining discussions with various entities about our statistical calculations and conclusions.

If you look just in the targeted population, and based on, you know, what we could collect in the targeted population, if we get 268,000 samples, just based on a straight statistical calculation, if there are five cases in that targeted population, then we should be able to find those sampling at that level.

There is lots of different ways to extrapolate that data to the broader cattle population. We've looked at probably at least three

of those and played with different ways to do that. There you can do sort of a ratio comparison, based on what they've done in Europe, where you are 29 times as likely to find disease in the targeted population as in the clinically-normal, and you sort of work that ratio and you can extrapolate information out.

John Wilesmith and Roger Morris have developed a computer model to look at surveillance data. We are also playing with that and plugging numbers into that. Our folks at Harvard, that have worked with this in the risk-assessment model, have suggested a couple of different ways to extrapolate data. All of those really get you back towards a one-in-a-million type level in the total population.

CHAIRPERSON PRIOLA: One final question from Doctor DeArmond.

DOCTOR DeARMOND: Whenever we try to do this work, we are criticized on exactly having the correct area in the obex region.

DOCTOR FERGUSON: Uh-huh.

DOCTOR DeARMOND: Do you rule out - when you make an IHC declaration of positivity or negativity, do you always have to include the nucleus of solitary track, the dorsal nucleus, the vagus and the trigeminal - descending trigeminal nucleus,

because that's where we are always criticized, because that's the hottest area, and down into the reticular formation is often a later stage of disease.

So, do you - when you make your declaration, is it when you have seen those three structures, or at least one or two of those structures, in your IHC?

DOCTOR FERGUSON: My understanding is, we are not necessarily having to look at all of those structures, I mean, if we see something that's lighting up and it is an appropriate location, we are going to call that positive.

I guess -

DOCTOR DeARMOND: Those structures should be included in your sample.

DOCTOR FERGUSON: Yeah, absolutely, and that's one of the big advantages that we feel with using IHC, is you can look at that and, hopefully, you know, if your tissue is not a total mess, you know, you can still see some of that tissue architecture and know that, yes, you are in the right place.

Al, do you want to weigh in there, yeah or nay?

DOCTOR JENNY: Yes. The samples are surprisingly good, for the most part, the ones that

are collected fresh and put on ice packs, are very good, and we see the level that we want to see of the obex.

CHAIRPERSON PRIOLA: Okay, all right, thank you very much, Lisa.

Okay, so we'll get on now to topic one, and to present that topic is Doctor Weinstein from the FDA.

DOCTOR WEINSTEIN: Okay.

I think we'll go to the next slide, please.

In this section of the meeting, we will discuss the possible risk of variant CJD, the patients in the United States who were treated with a Factor XI concentrate in investigational new drug studies, performed between 1989 and 1997.

The coagulation Factor XI concentrate was manufactured from the plasma donors living in the United Kingdom. We are looking for the Committee's advice on a risk assessment model that describes potential exposure of these patients to variant CJD.

I'll give a very brief overview of this issue. We will then hear more in-depth presentations from speakers from the U.K., the FDA, and the CDC, followed by questions to the Committee.

Now, in September of 2004, officials of the United Kingdom notified patients with bleeding disorders and congenital anti-thrombin III deficiency that they might be at increased risk of variant CJD. The products used by these patients were manufactured between 1980 and 1998, with a final out date of 2001. In 1999, U.K. plasma was no longer used to manufacture these products.

The reason for the increased concern in the United Kingdom about the transmission of variant CJD through plasma derivatives was the observation that the disease was probably transmitted in two cases, through transfusion of non-leukocyte-reduced red blood cells. The two donors of these cells developed variant CJD subsequent to their donations. U.K. donors of blood in plasma in general are at increased risk of variant CJD infection from eating BSE-infected meat.

Now, patients in the U.K. who received plasma-derived coagulation products and anti-thrombin III were advised not to donate blood, organs or tissues, to inform their surgeons and dentists of their increased risk so that special arrangements can be made for surgical and dental instruments to control potential infection, and to inform their families so

that surgeons could be told in case of emergency surgery.

Now, in the United States, there was no licensed product made from U.K. plasma. However, a small number of Factor XI deficient patients, and we estimate the number to be on the order of 50 or less, were treated under several IND protocols with Factor XI concentrate derived from U.K. plasma. No Factor XI product used in the United States was manufactured from any donor known to show clinical symptoms of variant CJD. Over time, however, we may find some infected individuals who did contribute to the manufacturing pools.

Now, with regard to Factor XI utilization, Factor XI is in the category of a very rare bleeding disorder. Literature estimates are on the order of 1/30,000 or 1/100,000,000. There is a much higher prevalence in certain population groups, including Iranian Jews, Ashkenazi Jews, and French Canadians.

The physical manifestations of the disease are rare, and the disease may be unrecognized until bleeding occurs associated with surgery, trauma, dental procedures, or menorrhagia.

Most of the Factor XI products studied under IND was used in one or two situations per

patient, to prevent excessive surgical or dental bleeding. This very infrequent use is in contrast to the use of plasma derivatives, like Factor VIII or Factor IX to treat the hemophilias.

We'll now have an in-depth presentation of the models and actions taken in the United Kingdom and the United States. Doctor Soldan, from the U.K. Health Protection Agency, will talk about the methods of risk assessment and assumptions used to develop a risk assessment model in the U.K.

Doctor Molesworth, also from the U.K. Health Protection Agency, will discuss actions taken in the U.K., based on their model.

Then Doctor Stephen Anderson from the FDA will present an assessment of possible risk of variant CJD from the Factor XI product used in the United States. This will be followed by a discussion by Doctor Lynne Sehulster from CDC about current public health recommendations on management of surgical instruments used on patients with TSC or TSC risk.

As these presentations are being made, we request the Committee to keep in mind these proposals. We ask the Committee at the end here to comment on FDA vCJD risk assessment for Factor XI manufactured from U.K. plasma, with regard to the model as applied to

Factor XI, and to please give any additional information that is needed to improve risk assessments for this Factor XI product.

CHAIRPERSON PRIOLA: Are there any questions for Doctor Weinstein before we go on?

Okay, if not, thank you.

We'll move on to the next speakers, who are Doctor Kate Soldan and Doctor Anna Molesworth, who are going to discuss U.K. risk assessment methods and assumptions.

DOCTOR SOLDAN: Good morning, everybody. Firstly, thank you very much for the invitation to come and speak to you today and share the U.K. experience.

Can you hear me? Is that clear? Okay, can everyone hear now? Great.

Anna and I, as introduced, Anna and I work at the CJD section of the U.K. Health Protection Agency Centre for Infections. I'm speaking today mainly in my role there as Scientific Secretary to the CJD Incidents Panel, which is the committee that has guided our management of the vCJD risk to plasma product recipients, and a role I've held since October.

My colleague, Anna, worked throughout 2004

on the U.K.'s notification of recipients of vCJD implicated plasma products. Anna will present to you the details of that process that we went through.

In our presentation today, we are going to give you an overview of both the context and the process of the U.K. plasma risk assessment and notification in the U.K. I'll start by setting the context and the general approach to reducing the risk of iatrogenic vCJD in the U.K.

For us, the plasma products are one aspect of this risk, and our approach is in the context of the whole iatrogenic risk in the U.K., so I hope that in setting the context I will preempt to answer some of the questions you may have about why we did what we did about plasma products in the U.K.

Anna will then go on to present the methods and the assumptions of the plasma product risk assessment. Anna will show the methods, or at least the strategy, that we used for notification of patients considered to be at risk.

And, we'll just end briefly on mentioning the ongoing surveillance of vCJD in this patient group in the U.K.

You'll be familiar, I'm sure, with the U.K. epidemic of vCJD, and this is the latest observed

data and modeling for the vCJD deaths to the end of 2004, you see here that the quadratic model in statistics is the best fit now for this observed incidence to date, with a peak in the middle of 2000 and currently a declining incidence.

It assumes, generally, that the majority of these cases, and the course for this curve here, reflects exposure to the BSE epidemic, the primary epidemic.

Person-to-person, or secondary transmission is now secondary cause for concern. There are, of course, many uncertainties in both the transmissability and the extent of exposure via secondary routes, not to mention susceptibility of those exposed, and this means that the magnitude of any future epidemic arising due to secondary transmission is highly uncertain at the moment. However, from modeling, for example, on the transmission by contaminated surgical instruments, shows the uncertain assumptions, iatrogenic transmission can lead to ongoing levels of infection, even in the absence of a continuing primary epidemic due to BSE.

So, this gives the background to the U.K.'s public health response to iatrogenic vCJD,

which includes the epidemic I've just shown you, and also knowledge of a potential, but unknown, risk, both due to surgery involving contact with tissues known to include vCJD infectivity, and also due to blood.

It's recognized this great uncertainty regarding pre-clinical and also sub-clinical vCJD in the population in the U.K., and an awareness, unlike sporadic CJD, variant CJD cases are younger, and therefore in some ways more likely to pose a risk to others.

There is knowledge of pre-symptomatic prion accumulation in certain tissues, and as I mentioned there's a possibility of sustaining the vCJD epidemic in the U.K. population by secondary means.

Also as a background to our approach, was the expectation that many of the actions may need to be taken retrospectively as routes of secondary transmission are identified after the diagnosis of the case.

To address these needs, and suit that background, in 2000 the Department of Health established a U.K.-wide expert committed, called the CJD Incidents Panel, and the role of this panel is to advise on situations where there was understood to be some risk of transmission of CJD of all types between

patients through clinical interventions.

I'll spare you from showing you the network of all the committees and organizations involved in the U.K. public health response, but simply mention that this panel, which guides this response to iatrogenic risk, works very closely with another committee, which makes recommendations for infection control precautions prospectively in clinical care patients in the U.K.

So the CJD Incidents Panel has played a key role in the plasma product risk assessment and notification. Its thinking and its approach was developed also, and, in fact, quite heavily, with surgical exposure in mind. And much of the rationale is shared.

The panel understands that there's a need to take precautionary actions, particularly, when science and the evidence is weak or, in fact, lacking, and for surgical exposures it was recognized that the means to eliminate risk, be that by single-use instruments, complete decontamination for all patients, or identification of particular patients which pose a risk, was not an available option, but some action was needed, and the actions would very often require individual review of individual cases.

One key principle you can see from all this is that in the CJD Panel's thinking and actions has been of risk reduction rather than risk elimination, and also the balance between risk reduction for public health purposes with some consideration of disproportionate efforts to achieve that and adverse effects for individual patients.

The panel advises on reduction of iatrogenic risk for a range of patients, for all patients with symptomatic disease, and also a number of groups of individuals who are asymptomatic and considered at risk of CJD, including variant CJD.

Plasma product recipients at risk of variant CJD come into the penultimate group listed here, along with patients exposed by potentially contaminated surgical instruments, and also by fresh blood transfusion.

The surgical exposure, the panel was guided in its actions and its recommendations by risk assessment conducted by the Department of Health that modeled the risk of transmission with repeated use of instruments that had been used on different tissues in individuals thought to harbor CJD infectivity.

The example model shown here is for CNS tissue, and with an assumption of 10 percent transfer

of residual tissue on the instruments. Then you can see, that's the dotted line here, the risk - you see the risk fall away with repeated use of instruments. This is the risk from 100 percent down to zero, and repeated use of the instruments. And, by the sixth patient, you see here the modeled risk falls around or below a 1 percent additional risk of infection.

In our risk assessment, the infectivity has been expressed in ID50s, which is the dose that is thought to lead to 50 percent of those exposed becoming infected. Based on those surgical models, the panel chose to consider patients to be at risk of vCJD or CJD due to surgery if their exposure equated to .02, ID50s, or a 1 percent additional risk of infection of both the population risk due to the surgical exposure or their potential surgical exposure.

This same threshold was used to determine the plasma product recipients to be considered at risk in the subsequent plasma product risk assessment and notification.

So, what happens to these patients who are considered to be at risk? They are advised, given a package of measures to reduce the risk of transmission. In fact, you have seen these already,

but the patients are asked not to give blood, not to donate tissue, and also to enable the medical staff to take certain precautions with the instruments used on them in surgical interventions.

In addition, clinicians were also asked to play a role in this in ensuring that infection control precautions are taken when these patients go for treatment, and also to review their previous medical history to identify if there are any other incidents that may have exposed patients that would also need similar control procedures to be applied.

Just to show you the prospective infection control recommendations that are made, what they actually lead to, they specify that in general instruments in contact with high or medium-risk tissue, as shown here, for this column of individuals the plasma product recipients would be at risk of iatrogenic, and for those patients it is generally advised that the instruments should be removed from use after use on the patient. And, of course, this can be both costly and disruptive to services. So, this is experience we are gaining in applying these guidelines currently.

Now, I want to move on specifically to the plasma products, and where theoretical risk assessment

was conducted in 1997. This was updated in 2003, both to incorporate new evidence, and also to move towards an assessment tool that could be applied to plasma pools containing implicated donations for immediate actions in the U.K.

The CJD Incidents Panel considered these risk assessments and developed and consulted on a mechanism for approaching these patients and the package of advice that they should be given. And then, as you know, in 2004, with two reports of probable transmission of vCJD infection by blood transfusion, that is of recipients transfused with blood from cases, this precipitated the move in the U.K. to trace and notify recipients of plasma products that were identified as at an increased risk.

Here I'll hand it over to Anna to take you through that process.

DOCTOR MOLESWORTH: Hi.

So, where are we? We've got, in 2004, two reports of probable transfusion-associated transmission, and we've also got framework for handling - for managing the risk in those patients, in terms of the public health precautions that need to be taken.

When the first case was announced at the

end of 2004, we immediately addressed the risk of transmission of variant CJD infection to other people who had been transfused implicated blood components, and we did that at the end of 2004 - 2003, and the start of 2004.

In addition to the components recipients, we also, obviously, had the radical risk of transmission of variant CJD through plasma products, and we had the DNV risk assessment, which had already been considered. We had a framework, again, to operate within, and we also had had a tool developed by the U.K. Department of Health which actually took the results of the DNV risk assessment and had made the first steps to translate that into assessment of individual risk.

At the start of 2004, we obviously were handed over the task of implementing the public health precautions, and I'm going to take you through that. But, you see DNV aren't here to present the risk assessment, and they are in a far better position than I am to actually explain the detail. What I'm going to do is just outline how it was used in terms of the U.K. notification and take you through that in further detail.

Okay. So we've got the DNV risk

assessment in three stages. It looked to infectivity in blood, infectivity in plasma fractions, and then also provided a tool for assessing batch risk and individual exposure to variant CJD.

So, to start off with, DNV reviewed all the experimental research available on the infectivity of blood and its components, and they produced a value of infectivity in one unit of blood. This is taken straight out of the DNV report. It gives you the various experiments which they considered, which you can find in the DNV report, so I'm not going to go into detail, and also the proportion of infectivity, which you'd expect to find in the various blood components as a result of these experiments, and the three main blood components being the red blood cells, the buffy coat, and also the plasma.

Now, there were a number of experiments. The main experiments which DNV focused on were the experiments by Brown, et al, in 1998 and 1999. in terms of reviewing the infectivity in the unit of blood, they actually focused on Brown's experiments in 1998, and in 1998 Brown conducted two main experiments, the low-dose endogenous experiments and also experiments which used spiked material.

The low-dose endogenous experiments looked

at the distribution of infectivity in the blood for mice who were inoculated intracerebrally, but with a mouse-adapted human TSE.

The spiking experiments looked at the distribution of infectivity in blood components in human blood, which have been spiked with bone material from scrapie-infected and scrapie-diseased hamsters, so two main experiments.

The one the DNV decided to go with, which proposed would be the most suitable, were the low-dose endogenous experiments, and they looked at the distribution of infectivity and they came out with this just over half the infectivity which you'd find in a unit of blood would be found in the plasma component.

Okay. Then DNV actually assessed how that infectivity in the plasma might be distributed within the different plasma fractions. Okay. So, this is in two parts, there's a focus on this, which is again from the DNV report, this is the outline of plasma fractionation process. Effectively, you start with a very large plasma batch start pool, about 20,000 donations, and the plasma are separated into cryoprecipitate, from which you get the main clotting Factor VIII, and cryosupernatum, which the other

products made from including the other blood clotting factors, Factor IX, XI anti-thrombin, various immunoglobulins and albumin, and these are the main products, and they are for - they are for the main intermediates, although plasma is also used to make other products. The whole of the Det Norske risk assessment was based on the major clotting factors, immunoglobulins and albumin.

Having been sent through the fractionation process, you get various intermediate stages, and in each of these stages before you reach the final product you get a series of processes involving precipitation, centrifugation and filtration, heat treatment, depending on the actual product involved.

And then, once you get to the final product, that's, obviously, distributed into the vials of product, and used to treat a variety of conditions.

Having an idea of this, obviously, Det Norske wanted to see how this infectivity might be distributed, there again, refer to the experiments conducted by Brown, et al in 1998 and 1999. All these are Brown's experiments, and again, it's found in the risk assessment, and effectively they decided to go with the low-dose experiments, the mouse-adapted human TSE, and that was the rate of the infectivity was

distributed amongst different plasma fractions with, actually, a combination of Brown's experiments in 1998 and 1999.

And, in this figure, just as in the previous one, I just want to draw your attention to the huge variation between the different experiments and the types of infectivity you might expect to see in the different plasma fractions.

This is what they came up with, and I will actually go into more detail of the assumptions further on in this presentation, but they derived values for the infectivity in each component and fraction per unit of blood. They said if a unit of whole blood, 450 mls, has got about 950 ID50s per unit, 53 percent of that goes into plasma, and then within that the infectivity is apportioned to these variant intermediate plasma fractions, the greatest infectivity being found in the cryoprecipitate, and the straight cryosupernatant, and then other levels of infectivity in the progressively - the highest levels of infectivity being in the lower fractions.

Okay, so that's what they came up with, and that was effectively what we used for - those were the figures that we used for our patient notification exercise.

So, DNV conclusions, obviously, we don't know the level of risk of variant CJD infectivity in the blood of people incubating disease. It's entirely based on animal models, but they show that we may have infectivity present in plasma, as well as other components, and if the level of infectivity is as suggested by animal models then it may be sufficient to cause infection, and therefore certain plasma products could carry a risk of infection.

Okay. So then the next stage of the DNV risk assessment is they provided this tool for assessing the type of risk you might expect to find in product batches and had to translate that into individual exposure. Now, we took this, this is what our Department of Health were working on, we developed it slightly, but not a great deal. Effectively, this process we used to calculate the potential risk of variant CJD in our implicated product batches using this, the infectivity per unit in a product batch, number of donations, number of implicated donations in the plasma start pool, the fraction-specific infectivity, and the proportion of the fraction used to make a batch, those were the key inputs.

Having got an idea of the individual batch risk, then what we needed to do is, obviously, assess

the individual exposure risk, so you get to the total infectivity in a product batch, the dose that individual would have received, from that, overall, the batch an individual would have received, and that will give us an idea of the kind of levels of potential infectivity that are out there, and, obviously, getting back to Kate's 1 percent threshold, the potential exposure to .02 ID50 is equivalent to our 1 percent risk of infection.

So that was the basis, that was the theoretical basis upon which we did the notification.

Now, clearly, there are a great many assumptions and uncertainties in that process. The main ones - well, they can be summed in three sections, the infectivity of blood relating to the processing, and also the susceptibility of individual recipients to infection. Now, certainty where there was uncertainty the most precautionary option was used, when there was uncertainty throughout, basically, throughout this entire process, we took a very precautionary approach, within the context of the background risk from dietary exposure to BSE, and this approach is basically traditionally used by the U.K. National Blood Services.

And, I guess that's with the view that

measures could be relaxed, should we get new evidence indicating that the risk had been overestimated by several orders of magnitude.

Okay, so I'm going to go through each of those - each of these assumptions.

Okay, relation to the infectivity of human blood. So, we are assuming that blood from somebody, incubation variant CJD is infectious. I think that's a reasonable assumption. We've had two reports of transfusion-associated infection. Statistical analysis indicate that the case of infection in a recipient of blood from a variant CJD-infected donor is unlikely to have occurred by chance, and we've had two instances of transmission of infection.

The other issue is right, okay, so we'll assume it's infectious, how much infection do we actually have in human blood? There's a massive range of levels of infectivity in human blood, I think it ranges between about 300 and 400 ID50. Experiments from Brown indicated that actually the level of infectivity might be towards the low end of the spectrum, and that Det Nortske's factors took the figure of ten as an appropriate level.

Then, additionally, experiments of Brown also indicated that the actual intravenous inoculation

of infectivity may be five times less efficient than through the intracerebral route, so they reduced that down to two, although it may be up to 100 times and this may again be an overestimate, but again, even if we had two intravenous ID50 primarily to human blood there's great variation around that estimate.

Okay. The second one, infectivity is constant throughout the incubation period, and is in presence at the time of donation, and as far back as 1980. In the U.K. we use 1980, as that's the time when we feel that BSE first entered the human, could have first entered the human food chain. So, that's why we use the start date of 1980.

So infectivity is constant throughout the incubation period, and nobody really knows, the experiments from Brown, which looked at pre-clinical distribution of infectivity, showed that there was very little. You couldn't detect the infectivity in pre-clinical stages, but that it showed up as soon as the mice became symptomatic. So, the chances are that that is probably not the right assumption, and the infectivity will increase the closer you get to onset of disease.

This one is very important, that the infectivity in blood components and plasma factions

varies from the vary for whole blood according to the ratios determined from endogenous low-dose experiments using blood from mice innoculated with a mouse-adapted human TSE. So, we are saying that Brown's experiments are directly applicable to the human situation. And again, as I showed you before, there was wide variation in the levels of infectivity found in the different plasma fractions.

We also did in it in clinically-ill mice in Brown's experiments, and they are also using a mouse-adapted human TSE, which is Gerstmann-Straussler-Scheinker syndrome, which although no relative percentage of other forms of CJD we are not sure how that translates to variant CJD.

Okay, and then the fourth one, leucodepletion doesn't reduce infective geoplasma, basically, that was evident through the review of experimental evidence, the infectivity may be present in components without white cells.

Okay, so that's the relating to the infectivity of blood, and we got the effects of processing, or processing-related issues.

In the U.K., we've got this background risk from the BSE epidemic, dietary exposure. We are only looking at the specific number of implicated

donations in the plasma start pool. We are only looking at donations from people, from donors, who are known to have gone on to develop variant CJD.

There's no cross-contamination during manufacture.

Every fraction manufactured could contain the potential levels of infectivity found per unit fraction of blood. We are, basically, saying that the figures that are presented to you from Brown's experiments, or derived from Brown's experiments, those could end up in the plasma fraction. We know that that's not possible because not the same amount of every plasma fraction is used in the product of each batch, so there might need to, again, be an overestimate.

We also assumed there was no reduction in infectivity through processing beyond fractionation or through storage, which is unlikely. There are, basically, three different approaches which were considered at this level. There was no evidence for the apportioning of infectivity according to protein content, which is one of the approaches considered in the Det Norske report.

Experiments on naturally-infective plasma, the endogenous experiments showed the infectivity

falls below the limits of detection early in the process, and that could be because of the low sensitivity of the test, but also the very low levels of infectivity present. The alternative to the endogenous experiments, the spiking experiments, we felt the behavior of infectivity as shown by the spiking experiments may not be the same as in endogenous infections.

Now, the U.K. - the Incidents Panel, our Incidents Panel, decided that either we could go with the spiking experiments, which did show successive reduction beyond fractionation, or we could go with the endogenous experiments, which dropped so low we couldn't detect it. Either would be justifiable. We actually went with the measure of infectivity in the plasma fractions of animals with endogenous infection and assumed no additional clearance after that. So, there's no clearance beyond fractionation. That's the worst-case scenario. It's unlikely that that is the precautionary approach we took in the U.K.

Okay. So then we go on to the susceptibility of recipients. Okay. The dose response for infectivity is linear, so, okay, we say we've got one ID50 is 50 percent risk of infection, the .02 is 100 percent of the risk fraction,

therefore, .02 is the 1 percent risk of infection.

The risk to patients is additive over their lifetime of exposure. Now, animal models have suggested that the cumulative effect of regular doses is actually less than the effect of a single cumulative dose, so to speak, and actually, when Det Norske Veritas were developing their risk model they decided that they would look at exposures, human exposures, up to a period of one year, and then forget the rest. We took a more precautionary approach, and we just said, cumulative exposures over a lifetime, and that's what we looked at.

All recipients are equally vulnerable, well, we, obviously, did not take into account genotype, of which all cases of CJD have been methionine homozygous, although we have had this one instance of transmission of infection to a heterozygote, no strain variation, no discrimination by age. We took into account no host factors.

And then the final assumption was, obviously, that animal models are applicable to humans, and, particularly, in relation to variant CJD.

Okay, so that's how we used the DNV risk assessment.

So then, it was how do we translate this

into action? We've got a process for estimating batch risk, and individual risk, should we want to take that approach, and we've also got this framework. So, as Kate was saying, the CJD Incidents Panel has advised that patients who are exposed to a 1 percent or .02 ID50 or greater potential risk of infection by surgical exposure, or exposure to plasma products, in addition to the background risk from potential dietary exposure, should be considered at risk of variant CJD for public health purposes. And, it was a very important thing, this "for public health purposes," although we've had these two cases, two instances of transfusion-associated transmission, we've had no case of variant CJD in any patient regularly receiving plasma products in the U.K., and we simply don't know how the risk of exposure to infectivity actually translates to the risk of developing CJD.

Okay, so these patients are at risk for public health purposes, and we needed to advise them of the special precautions that they needed to take.

Okay. So, the first stage, the National CJD Surveillance Unit in Edinburgh, handles the surveillance of variant CJD in the United Kingdom, and our National Blood Services, obviously, consider the donor population. They have a study called the TIMER

review, which actually is used to identify blood donors who subsequently develop variant CJD, and, in fact, what happens is that all variant CJD cases are actively investigated for history of blood donation or transfusion, and the implicated donations are identified.

Now, when we launched this notification in September last year there were nine donors, there are still to our knowledge nine donors who subsequently developed variant CJD who donated blood for fractionation.

Having identified those donors, we identified plasma sent for fractionation, and there were 23 donations of plasma sent for fractionation, and then working with the product manufacturers we identified the batches of plasma product or intermediate made from the implicated plasma, and thereby the estimated dose equivalent is 1 percent risk. And again, we had to take 187 batches of product and intermediate from these 23 donations from these nine donors, and that situation still holds today.

Okay. The next step was, obviously, to estimate the infectivity calculated using the process I've just described to you, so that's using the DNV

risk assessment and also the batch specific manufacturing data from the manufacturers, and what we managed to do was to look at each of the products which had been implicated, so we had Factor VIII, Factor IX anti-thrombin, immunoglobulins now being 4.5 percent, as well as these other products. The intermediate excipient is used as a vehicle or stabilizer in the final product batch, so with Factor VIII, the actual factor concentrate here wasn't implicated, the albumin that was used to stabilize that factor in the vial was implicated.

We looked at the infectivity for each of these batches, across 174 total finished product batches, rather than intermediate, and we looked to see, we looked at the sort of dose ranges that patients were likely to have been treated with in clinical practice, and then so comparing that with the infectivity to see how much of this product would actually be required to cross the threshold.

And, as a result of that, we managed to stratify each of these implicated products according to the likelihood of a patient who received those products passing the 1 percent threshold. So, with the Factor VIII, Factor IX anti-thrombin, that was high because a single dose, or a fraction of a dose in

the small - a fraction of a dose in the single-dose - would be sufficient to cross this threshold.

With these products, with some of the intravenous immunoglobulins now being 5 percent, there was a huge range in infectivity. It was feasible that some patients, if they had been exposed to certain product batches might have cross the threshold, but the majority of cases you would need these volumes of albumin, say, to cross the threshold. So, in most of these situations there wouldn't have been any risk, per se, in terms of our public health action, but they were still an important group to check, and with the low volumes required to have been so large that they would not have been right in clinical practice.

And the advice that we gave was that we made efforts to trace the high risk, we traced the high risk batches and the patients who received them, because only a single-dose - would be considered at risk, but the medium risk batches, again, we'd want to trace those products and actually assess the individual exposure to risk, and with the low risk factors the risk was negligible, and our advice was that the batches do not need to be traced.

And so, that's what we did. But, of course, the next stage was, obviously, assessing the

- was how we actually notified the patient groups, and we identified three main groups of patients. We had patients with bleeding disorders and congenital anti-thrombin III deficiency, as well as patients with primary immunodeficiency, who are regularly exposed to plasma products. Then you've got the other group of patients with a heterogenous group of other conditions, where they may, say through treatment of severe burns, plasma exchange or certain neurological conditions, be likely - be exposed to these products in the sort of one-off situation.

So, it's how do we best notify these people? Obviously, we developed strategies for each patient group in collaboration with the patient representatives, and also the clinicians treating them, so it really was an iterative process to reach a consensus.

But, the main factors dictating the final choice were, obviously, the likelihood of patients surpassing the threshold, the numbers affected how we actually traced the products and, obviously, the potential impact of the public health measures.

There were two main approaches. The population approach, which we took for patients with bleeding disorders, which was that all patients with

bleeding disorders and congenital anti-thrombin III deficiency had been treated with the U.K.-sourced pooled factor concentrates, or anti-thrombin between 1980, when BSE first entered the food chain, and 2001, which was the last expiratory date of any product made in the U.K. from U.K.-sourced plasma, should be considered at risk of variant CJD for public health purposes.

And, this is what we termed the population approach, and it was based on the fact that a single dose of implicated product in a small trial fraction - it should be the other way around, sorry - would be sufficient to place an individual recipient at risk, that not receiving these products may not necessarily mean exposure hadn't occurred, because future batches may be implicated. A large proportion of patients were likely to be affected, and also that the use of a cutoff, this 1 percent cutoff, implied the degree of scientific uncertainty, which given these other factors, and the context of care and the history of previous notifications of other blood-borne pathogens in this patient group couldn't really be justified, so that's why we went with the population approach for this group.

For all other patients, we went on an

individual approach, so patients with other conditions, who had been assessed to be over 1 percent, to have received a 1 percent level of infectivity, should be considered at risk, and the decision to do that was based on the fact that for most of these patients, most other patients, the products used to treat the conditions were such that substantial quantities would be required to place the recipient at risk, and, therefore, very few patients were likely to be affected, and that's been borne out, really, by the outcome of our notification, and also this approach was consistent with the approach used for surgically-exposed patients.

Okay. So, those are the two approaches.

Very briefly, this is what - this really summarizes who we will notify. We've got patients who received plasma products between 1980 and 2001. Recipients of non-U.K.-sourced products, no action needed, they are not in the equation here. Recipients of U.K.-sourced products are, or patients with bleeding disorders, patients with bleeding disorders and congenital antithrombin III deficiency between these dates, they were all considered at risk and they were contacted directly by the clinicians.

Patients with primary immunodeficiency,

between these dates, '96 and 2000, that was the dates in which the products were circulating, were also contacted directly by their doctors. Not all of them were at risk, they were individually assessed, but they could be handled by their doctors because there were clinical networks that support these patients.

It's with the other groups of patients, where it becomes, in a sense, more difficult, because there is no clear clinical network or patient support group to support these people, so the patients with immunodeficiencies, certain neurological autoimmune conditions, patients seen for severe bones plasma exchange, other patients who may have received prothrombin complex concentrates, you know, with acquired anti-thrombin deficiency or requiring rapid warfarin reversal, thus anticoagulation, these are the groups we needed to trace through the hospitals, and this is what we asked as part of the notification, was that these groups, the hospitals actually trace the implicated product batches down to individual patient level, and then we, at the HPA, assess their level of risk and get back to them with the action they need to take.

Okay, so that summarizes where the entire process underlying our work last year on the risk

assessment, and also the translation into public health notification.

I'll just hand back to Kate to wrap up.

DOCTOR SOLDAN: Just to very briefly, really, mention ongoing surveillance now has several strands. There is a study in place of patients with hemophilia, and this protocol involves collection of residual tissues taken during clinical curve, as well as requests for post-mortem during life to be granted.

Also, another strand of monitoring this risk, of course, is the National Surveillance cases, and review of that past medical history, to try and identify any exposure through plasma products.

We are also working on developing follow up for other at-risk patient groups, along the same lines as for the hemophilia patients.

And, of course, as always, all these methods have weaknesses and gaps in ascertainment, heavy reliance in the U.K. on astute positions physicians to pick up particularly unusual events in patients that they may think to be associated with exposure to CJD.

I need to acknowledge, you can understand the process of risk assessment and patient notification was no small undertaking in the U.K., and

I'm sure this isn't a full list of contributors, but we do acknowledge the contribution of many people in all of these organizations.

Thank you.

CHAIRPERSON PRIOLA: Are there any questions for either of the speakers from the Committee?

Doctor Telling?

DOCTOR TELLING: So you mentioned that some major uncertainty relates to the validity of using mouse-adapted scrapie and the effects of strain and other effects have been more or less ignored in determining risk. So, I'm wondering whether the work of Houston and co-workers, who have shown transmission of BSE in a sheep model by blood transfusion can shed any light on modifying the risk assessment?

DOCTOR MOLESWORTH: Again, this is why we need Det Norske Veritas to comment on this, but the work by Houston was incorporated into their risk assessment. It was one of the experiments that they actually assessed, and they decided to go with the work by Brown, but they did incorporate an awful lot of other information. And, yeah, I'm quite sure there are various different scenarios which we could look at.

DOCTOR TELLING: Okay.

DOCTOR MOLESWORTH: Yeah.

CHAIRPERSON PRIOLA: Doctor Schonberger?

DOCTOR SCHONBERGER: You know, public health often uses human epidemiology to make decisions, and I was wondering how you've used the tracing of recipients of the plasma products in your decision-making, and also the results of the study of hemophilia patients in the U.K., which I understand does not show any lesions in these patients indicative of prion infection. Is that not true?

DOCTOR SOLDAN: Well, on your second point, I mean that study protocol is in place, but there's not really - there's no power there, there's no findings as yet that would lead you to say one way or another. I mean, that protocol is in place, and being developed as we speak here today, but, you are right, there's no findings to indicate infectivity, but there's not been -

DOCTOR SCHONBERGER: I don't understand why there would be no power. You are saying that one dose, from 1980 onwards, would potentially put these people at high risk, how many people have been studied?

DOCTOR SOLDAN: Well, what I was referring

to was the collection of residual specimens in post-mortem in those people, that's not - we don't have numbers of those events yet. We don't have residual tissues collected and tested. We don't have post-mortem findings from those patients.

So, the protocol is set up to do that, but as yet it hasn't yielded very much.

DOCTOR SCHONBERGER: And, the follow up of - is the statement that there are no variant CJD cases amongst the group that have received these products from known vCJD donors a true statement still?

DOCTOR MOLESWORTH: That's correct, as we all know, I mean, the National CJD Surveillance Unit in Edinburgh would detect these cases. To their knowledge, there have been no cases detected.

DOCTOR SCHONBERGER: So, cannot that type of data be entered into your risk assessment, as to what the absence of cases, particularly, in hemophilia patients which would have -

DOCTOR MOLESWORTH: The whole basis of the risk assessment is precautionary. I mean, we have no cases in recipients of plasma products that we're preempting.

DOCTOR SCHONBERGER: Right, but can't you use - I mean, the worst case scenario would be

assuming that those individuals were not infected, what could still be the risk assuming - in other words, one could look at the absence of those cases and say there's no risk, we can forget about it. The precautionary approach would be, well, we've got those observations, let's assume worst case scenario, that they've avoided, by luck or some other reason, getting the disease, what would then be a risk consistent with the observation in humans? Has that kind of approach been tried?

DOCTOR SOLDAN: I mean, the statistical monitoring needs to go on from this point. We've not yet got the person years of exposure monitored that would exclude a level of transmission which is consistent with -

DOCTOR SCHONBERGER: With what he observations have been.

DOCTOR SOLDAN: Yes.

CHAIRPERSON PRIOLA: Doctor DeArmond?

DOCTOR DeARMOND: Yeah, sort of following up on that, but from just the basic data perspective. There's an assumption that there's two ID50 units in a unit of human blood, but can't that be measured? I remember a couple of years I asked this committee, has blood been looked at in detail, and I was told, or we

were told by some representative from the U.K., that blood was not allowed to be taken from these patients for such studies.

But, it seems to me we should be able to look at that at this stage and find out what the true ID50 is of human blood, of patients with variant CJD. That would eliminate a lot of all these assumptions.

The other aspect has to do with the various purification of fractions. The assumptions in none of your figures here of what it should be, the assessment in, I guess, a whole unit of human blood is based, I guess, on the animal studies.

DOCTOR MOLESWORTH: Yes.

DOCTOR DeARMOND: And, the question, even here the assumption is that the animal studies represent - the way they purify the fractions is identical to the way fractions are purified in the human case.

On the other hand, there's the techniques for detecting abnormal prion protein today are so sensitive, they are less than one infectious unit based on bioassays. Those fractions can be tested today to get a better marker of what infectivity is, what infectivity level may actually be there.

So, this is very confusing to me as a

neuropathologist, it's very intense, based on a lot of assumptions, and I can see that there is some real data that has to be obtained at this stage, and can be obtained at this stage. It's more, what are your comments on that?

DOCTOR MOLESWORTH: My comments are I agree completely. I mean, it's just based on the experimental data, it was updated in 2003 by DNV, but, yeah, I mean, you've got massive assumptions that human blood - we should have a far better idea of the infectivity in human blood, and also the reduction in infectivity through processing.

I don't know myself how sensitive the tests are to very low levels of infectivity, so I'm not sure -

DOCTOR DeARMOND: They are very good now, absolutely, the CDI assay is very - is superior.

DOCTOR MOLESWORTH: Yeah.

DOCTOR DeARMOND: It's a thousand-fold better than Western.

DOCTOR MOLESWORTH: Yeah.

DOCTOR SOLDAN: We don't as yet, am I right, we don't as yet have a test sensitive enough for testing bloods, so though that's the direction things are going, we don't yet have it.

DOCTOR DeARMOND: That's not true. There are - this has been presented at meetings in Europe and in the U.S., you can actually in sporadic vCJD cases you can detect abnormal prion protein in blood. It's not very much higher than controls, but you can detect it, but we have no clue as to what it is in a unit of blood from a variant CJD case.

DOCTOR MOLESWORTH: Yeah.

DOCTOR DeARMOND: And, that should be known at this stage.

CHAIRPERSON PRIOLA: Well, there's certainly been no proved test for detecting in blood.

DOCTOR DeARMOND: You mean approved test.

CHAIRPERSON PRIOLA: Yes, yes, yes, so there's nothing -

DOCTOR DeARMOND: There is a proved test, but not an approved test.

CHAIRPERSON PRIOLA: Right, right.

Doctor Salman?

DOCTOR SALMAN: Can you comment on what the range you used for the fraction-specific infectivity in your equation?

DOCTOR MOLESWORTH: In can't comment on the range for that, that comes out of the DNV report.

DOCTOR SALMAN: So, it's only from the

animal data, is that right?

DOCTOR MOLESWORTH: Yes.

DOCTOR SALMAN: But, you combined both the use of instruments and the blood donors, in the one risk assessment, is that correct?

DOCTOR MOLESWORTH: No.

DOCTOR SOLDAN: No, there's been two sets - there was a risk assessment done on surgical - contamination of surgical instruments, a separate risk assessment did on bloods and blood products. Is that your question?

DOCTOR SALMAN: Yeah, but you used the same threshold, is that right, of .02 ID50?

DOCTOR SOLDAN: Yes.

DOCTOR SALMAN: What's the justification for that, to be used for both?

DOCTOR SOLDAN: Well, when the surgical risk assessment was considered, I mean, it was based on the model of which I showed you one example.

DOCTOR SALMAN: Okay.

DOCTOR SOLDAN: And, balancing the practicality of tracing recipients - sorry, tracing exposed patients with the reduction of the risk. So, the cutoff was taken at a point which was felt to balance the number of patients to be contacted and

informed and managed in this way with the reduction of the risk. And, the 1 percent threshold was considered a pragmatic and public health sensitive threshold.

When the panel came to consider the plasma product risk assessments, the same threshold was applied in order to be consistent with the surgical exposure, and follow a consistent approach, in the absence of any real evidence that a different approach would be better.

DOCTOR SALMAN: And, it seemed like you have not done the sensitivity analysis to see how sensitive this type of threshold.

DOCTOR SOLDAN: I'm not sure I understand.

DOCTOR SALMAN: For the risk assessment, have you done any sensitivity analysis on some of the parameters you use in the equation?

DOCTOR SOLDAN: Did the DNV risk assessment includes sensitivity analysis?

DOCTOR MOLESWORTH: No.

DOCTOR SOLDAN: In think the range, it was always acknowledged that the uncertainty was great, and ranges were given around some of the parameters, but not on the cutoff.

DOCTOR SALMAN: Okay, thank you.

CHAIRPERSON PRIOLA: Doctor DiMichele?

DOCTOR DiMICHELE: Thank you.

In sort of pursuing the issue of getting tissue or getting evidence prospectively, could you describe the surveillance program for hemophilia that's underway, with respect to what tissue, in whom, are hemophilia A and B patients being looked at similarly, and is this going to be a voluntary or, you know, less voluntary program?

DOCTOR MOLESWORTH: Yeah, I can do my best. I don't know all the details of it myself.

The U.K. Hemophilia Centre Doctors Organization has a study which is set up to monitor exposure to variant CJD implicated plasma products in the patients on their register, and that register was, I think, set up about three years ago.

And, the patients currently on their register include hemophilia A and B and von Willebrand's disease, they don't include anybody else, so we are going - we are working with them to expand that, that protocol.

In addition to monitoring - to monitoring exposure to variant CJD implicated products, and, obviously, the outcome of that exposure, the long-term outcome in that patient group, they also have tagged onto that the information relating to the outcome of

tonsillectomies and, I think, appendicectomies, that have been tested by the National CJD Surveillance Unit in Edinburgh, and I don't know whether they test PrPsc-positive or not. The actual intricacies of how that mechanism works I myself am unclear on.

DOCTOR SOLDAN: In mean, I can just add a little bit to that I think. The protocol involves, certainly, informed consent or dissent to tissues removed during the course of clinical care to be referred for testing, and also consent or dissent in life to investigations afterwards. So, it is with consent.

CHAIRPERSON PRIOLA: Doctor Petteway, and then Doctor Belay.

DOCTOR PETTEWAY: Thank you.

Just a couple of questions relating back, again, to the assumptions made on process and removal, and I wonder if there was an analysis done of the process that was used by Brown, et al, when they did their studies relative to the fractionation process as it were used to actually make the products in that correlation.

And then the other is, you know, when you are informing someone of risk, I think a lot of assumptions went into this, but one of the key

components of assessing risk for pathogens, certainly, for viruses, has been removal or inactivation during a specific process. And, not to include that probably doesn't allow you to inform whoever you are going to inform of a more holistic sort of approach to risk.

And, I think, I mean, this is a very good approach, and I think you've done a great job, but leaving that out and not applying it probably doesn't give you a good idea of risk for each product, and I just wonder, you know, what were the components of that discussion, and why did that get left out?

DOCTOR MOLESWORTH: In mean, issues like this were thrashed round and round various committee tables over about a nine-month period. I can't actually tell you why it ended up like that. I'm not quite sure. I think the important message is not so much to focus on individual risk, but to look at the relative risk of each product in relation, so that I would be happy saying that they clotting factors are higher risk than the immunoglobulins and the albumin. But, in terms of the actual batch specific infectivity as calculated, yes, there are huge numbers of assumptions, and they cannot - I mean, if you look at the assumptions you know that they cannot be right in themselves.

We really did try and convey that message when we were notifying the patients, we said you are at risk for public health purposes, but we don't know how this translates to your risk of actual exposure to infectivity or to developing CJD.

I mean, it's very difficult to get that message across.

DOCTOR PETTEWAY: In appreciate that, and that was, you know, the basis of my question, and so you did clarify that as you made your communications.

DOCTOR MOLESWORTH: Yes.

DOCTOR BELAY: I was just curious about the total estimated number of patients that have been notified, and whether or not discrimination in clinical care, for example, was a problem.

DOCTOR MOLESWORTH: Okay.

There were about 6,000 patients with bleeding disorders notified of the situation, of whom about 4,000, we estimate, fell into that - into the at-risk category under the population approach.

And again, our U.K. Hemophilia Centre Doctors Organization is collecting the data so they will be able to provide some more up-to-date figures on the actual numbers who were placed at risk in that group.

In terms of patients of primary immunodeficiency, there are no patients, to our knowledge, or to the clinical networks, who undertook the assessment who have been placed at risk. So, not one patient with primary immunodeficiency who received repeat doses of intravenous immunoglobulin received sufficient to be placed at risk.

In terms of the other patients, we have - we've been collecting information on those patients and performing the individual exposures, we've received, I think at the end of last year we'd received about 19,000 - 1,900 exposure assessment forms, of which I think it was about -

DOCTOR SOLDAN: About a dozen.

DOCTOR MOLESWORTH: Yeah, about 12 patients who'd been actually placed at risk, most of whom had actually received the anti-thrombin III or the prothrombin complex concentrates, and only about three of them had received sufficient albumin to be placed at risk.

Okay, so we are dealing with very small numbers there.

DOCTOR SOLDAN: So, the bulk of the impact in terms of clinical care is with those 4,000 hemophilia patients, and at after examining some of

the issues we're working through with quarantine of instruments and, therefore, the services those patients may have, whether the services would be in any way compromised by the need to quarantine instruments after procedures on those patients. And, that's something we are working through at the moment.

There doesn't seem to be a huge crisis as yet, but, of course, there are certain areas of healthcare that are raising concerns about the cost of quarantine and the implications for service.

But, there are ways to manage that, which we are trying to develop now, in order to minimize the impacts, both on those patients and on other patients.

DOCTOR BELAY: Do any of your at-risk patients include Factor XI recipients, because that's what this Committee is considering today.

DOCTOR MOLESWORTH: Those patients, if they exist, will be encompassed under our population approach to patients with bleeding disorders, but remember, we - the whole notification that we dealt with was based on implicated products, products which had been implicated by a donation from a known donor who subsequently developed variant CJD. Factor XI was never implicated, it was only Factor VIII, Factor 9 and anti-thrombin that to date have been implicated.

CHAIRPERSON PRIOLA: Doctor Allen?

DOCTOR ALLEN: Thank you.

When I first put up my hand I had wanted to get into this area of recipient notification, and you've answered some of the issues. Can you tell us a little bit about the response of the people? You already commented on the difficulty, obviously, of conveying what the actual degree of risk is, and could you also comment on what the reaction of physicians is, since you are using the primary care physician for notification, as we would probably do in this country, and I think the difficulty of trying, in my view, to bring primary care physicians up to speed in terms of how to do the notification, and what to say, is probably equally as difficult as notifying the patients.

DOCTOR SOLDAN: I'll start, Anna, maybe you can add some points.

I mean, I think this process is still very much in process for us, so it's a little bit early to feed back to you the response from the patient group on the whole. I mean, we are having early and ad hoc responses, but we've as yet not investigated, particularly, not investigated patient response, and not greatly clinician response either.

After the notification of recipients of blood components, which was a much smaller group, that was the first notification of this type that we did, we did a survey of the clinicians who did that notification, and whether they found they were the appropriate people to deliver the notification, and whether the patients found the information acceptable. And, on the whole, that was the message that came back, that the primary care physician was the appropriate person to deal with this situation, bearing in mind it's going to be a chronic one, and also that in general the patients accepted the information fairly stoically.

We don't as yet have any - and, obviously, it's a much larger group, and so in discussions we've been consulting with social science colleagues in order to do some study of the response of the patients in this larger group.

CHAIRPERSON PRIOLA: Doctor Bracey and then Doctor Schonberger.

DOCTOR BRACEY: Actually, my comment related to what Doctor Allen was commenting upon, and that is the great degree of difficulty in training the communicator. We have experience here with CJD, tremendous problems in terms of the vCJD travel

restrictions in terms of training the communicator, the primary physician. So, I would just caution that they will be a tremendous undertaking.

DOCTOR SCHONBERGER: In wonder if you could clarify again how you are handling the Factor XI recipients who, of course, as you say, have not received product linked to a known vCJD donor, but I saw that you were regarding them potentially at risk, but you are not - can you clarify how you are handling that again?

DOCTOR MOLESWORTH: This is correct.

Patients who receive Factor XI are included under our population approach. All patients with bleeding disorders who received U.K-sourced plasma between 1980 and 2001 are considered at risk, and, therefore, they are being handled in exactly the same way as every other patient within that umbrella, regardless of whether or not that patient received an implicated product. So, they will be treated the same way as a patient who received five vials of implicated Factor VIII, either be approached by a clinician, they will be told there is this possible potential risk of variant CJD infectivity that they may have received through plasma products, and that they are asked to take these special public health precautions to reduce

the possibility of onward transmission.

DOCTOR SCHONBERGER: But, that hasn't been done yet, and we don't know how they've reacted, is that - I was trying to figure out what your answer to Doctor Belay was.

DOCTOR MOLESWORTH: It has been done, that was the patient notification that took place in 2004, but as Kate was saying, we have not - we do not yet know what the individual patient responses have been to those patient notifications.

DOCTOR SOLDAN: It's, perhaps, important to clarify there that it's only patients with bleeding disorders who come under that population approach. So, a patient without a bleeding disorder anti-thrombin deficiency, who had received Factor XI in the U.K., is currently non-notified. Is that your question? Because they've received no implicated product, and they don't come under the population approach.

CHAIRPERSON PRIOLA: Doctor Epstein, do you have a comment?

DOCTOR EPSTEIN: Yes.

I have two questions, first for Doctor Molesworth. Could you just clarify for me, when you look at the estimated threshold for receiving .02

ID50, and then you determine whether a patient is or is not in the at-risk category, is that based on their historic product use, or does it include some effort prospectively to look at their likely product receipt, say, over a year or over a lifetime?

DOCTOR MOLESWORTH: No, it's only based on the information that we receive on exposure to the specific implicated product batches.

DOCTOR EPSTEIN: SO, how much implicated product did the patient receive is the question you try to answer?

DOCTOR MOLESWORTH: That's exactly it, yes.

DOCTOR EPSTEIN: Okay.

And, looking at these numbers, am I correct to conclude that for clotting factor and AT3 patients receipt of an individual dose would be likely to exceed the threshold?

DOCTOR MOLESWORTH: Yeah, that's correct, and that was one of the factors which fed into this population approach, was it because such low doses were received, and because vials of this stuff were distributed throughout the U.K., a large proportion of individuals were likely to have been affected.

DOCTOR EPSTEIN: And then, my last question is, could you comment whether the tissue surveillance

studies that have provided a finding of, roughly, three positive appendices out of 12,000 surveyed, suggesting that there might be a higher level of latently incubating infection of the population may affect these estimates that we've been hearing? In other words, in light of the tissue survey, has there been any effort to reexamine the risk estimates, for instance, in pools of 20,000 you might, first of all, expect a much higher frequency of contaminated pools, and secondly, the risk of multiple positive units contributing to a pool is not trivial if those rates are, in fact, real.

DOCTOR MOLESWORTH: I'll pass this on to Kate, but the main message I think is important to get across, we've got a different situation in the U.K., because we have this background risk to exposure to variant CJD, so that, we didn't consider the possibility - I mean, yes, we recognized that there will be in the future other donations who will become implicated, but didn't factor that into this risk assessment, because we are already sitting on this background risk, where everybody in the population is being exposed. So, no, we didn't incorporate that.

If you want to say something more.

DOCTOR SOLDAN: Yeah, there's not much to

add. I mean, the answer is no, in light of the prevalent studies these risk assessments have not been - not as yet been redone.

CHAIRPERSON PRIOLA: In think we'll have one more question and then we'll move on.

Doctor Nemo?

DOCTOR NEMO: I'm still unclear on how you treat the Factor XI recipients. Now, they've never received any implicated lots, but what public health message are you giving to them? Are they not to donate blood as well?

DOCTOR MOLESWORTH: Yeah, that's correct, because Factor XI recipients, under the population approach for patients with bleeding disorders, same as any other patient with bleeding disorders who is incorporated in that approach, not to donate blood, tissues, organs, to inform their medical carriers and dentists, and also to tell their families.

CHAIRPERSON PRIOLA: Will both of you be here for part of the day, or the rest of the day?

DOCTOR MOLESWORTH: Yes.

CHAIRPERSON PRIOLA: Okay.

So, if there are anymore questions from the Committee members, especially during our discussion period, they'll be around to answer them.

So, keep those questions in mind.

So, with that, we'll move on to Doctor Anderson, from the FDA, who is going to provide us with the risk assessment for Factor XI.

DOCTOR ANDERSON: All right, good morning. My name is Steve Anderson, and I'm the Associate Director for Risk Assessment, in the Office of Biostatistics and Epidemiology, at the Center for Biologics Evaluation and Research.

Today I'm going to talk about a draft risk assessment that we have for U.K.-manufactured Factor XI and potential variant CJD exposure.

All right. Now, generally, FDA follows this four-part framework for risk assessments that we conduct in the Agency. The framework was initially developed by the National Academies of Science. The four elements shown in this slide consist of hazard identification, dose response, and that's also known as hazard characterization in some certain other frameworks, exposure assessment, and then risk characterization.

Now, just for brevity purposes, I've put brief descriptions for each of these components, but I think I'll hold off the explanations for each until I get to those portions that I describe in the risk

assessment.

So, I have a lot of caveats in my talk, because I think the main wall about what we are going to be talking about here is quantitative risk assessment, and if anything you take away from this risk assessment process is uncertainty.

So, commonly, what we do is we use risk assessment as a process, when uncertainty about a risk is particularly high. Uncertainty, again, is pervasive throughout risk assessment, so everything that I say there's a degree of uncertainty in the calculations, in the assumptions we make, and in many of the components of the risk assessment that I'm going to describe.

Just for sort of a clarification, because you hear this term, risk assessment, a number of times, I'm going to be describing our risk assessment, and our risk assessment, actually, consists of two components. It consists of a model, in this case a computer model that we've done, that contain all the calculations that are contained in this document, and then the document is a summary of those mathematical equations, and it's organized according to the National Academies of Science framework.

So, that's just for a simple

clarification.

Now, more about quantitative risk assessment. I'm just going to sort of briefly go through some of these.

The purpose of quantitative risk assessment is to link the relevant data together in a meaningful way. We are trying to estimate potential exposure and risk, and I think one important thing here is that there's going to be a heavy reliance and emphasis on exposure and less on risk, because we are more - although we have a high degree of uncertainty, we are more certain, or there's less certainty, let's say, about exposure, and a high degree of uncertainty about estimating risk. So, we are going to emphasize sort of the potential exposure and exposure assessment aspects in this model.

Also, risk assessment provides us framework to identify critical elements where research will improve the model. It's also an important process in understanding key elements, that what we say is the elements that drive the risk, or heavily influence the final risk estimate. And then, I think it's important to remember that this is an iterative process, so, you know, the document that's been submitted and that you are seeing is really sort of the first part of this

whole process, and we are going to probably be - well, not frequently, but we are probably going to be updating this model as new data and information, and we conduct a peer review process on this model, go on.

So, this is really just a starting point or a jump-off point for the next stages in the process, so let me move on to the draft risk assessment for Factor XI and variant CJD.

Okay. So, what we've got, actually, I've got this long question here, so given the probable - the recent probable transmission of variant CJD via transfusion of non-leukocyte-reduced RBC concentrates, or red blood cell concentrates, the important question for me is here as a risk assessor, what is the risk to U.S. recipients that received human plasma-derived Factor XI product from 1989 to 1997 that was manufactured from U.K. plasma? So, that's the question that gives this risk assessment its scope and its shape. We are interested in this risk from this product that was manufactured in the U.K., and was used in the United States during this 1989 to 1997 period, as Doctor Weinstein said, under investigational use.

Okay. So, Doctor Weinstein has also given us some background about Factor XI. Again, it's a

clotting factor present in low concentrations. The deficiency is rare. Bleeding is less frequently observed than that of other hemophilias, especially A and B, and bleedings associated with surgery.

All right, so, all right, I'm going to start sort of just walking you through these components that we've applied this risk assessment framework to for the Factor XI risk assessment. So, I'm going to start with hazard identification.

Hazard identification is this in-depth review of the available data and information. So, we've done an exhaustive, or extensive, literature review, pulled in all the information that we had available to us, and what that information does for us is it establishes - we try to establish a causality between the hazard, which is the TSE agent in blood, and then infection or illness, what's the possibility or risk that we could have vCJD infection caused by this hazard of TSE or vCJD agent in the blood, or what's the possibility of illness?

Sort of just rapidly moving on, these are the kinds of things, although in the risk assessment you'll see there's much more detail that we include, so we have two recent cases of probably transfusion transmitted variant CJD in the United Kingdom over the

past year and a half. Now, that raises this possibility of transmission of variant vCJD via plasma-derived products. And, I think it's important to emphasize this last bullet point, which is, to date variant CJD transmission via plasma derivatives has not been observed, and that's significant, and I'm going to discuss that a little bit more in detail in a moment.

Any time you see this bullet point sort of highlighted, this is pink or orange, Factor XI risk assessment, I'm specifically talking about the risk assessment. I'll also be making some general points about risk assessment in this talk, too.

So, in the Factor XI risk assessment, we considered vCJD transmission via Factor XI as a potential hazard. So again, we haven't really observed cases or transmissions via Factor XI of variant CJD, but there is a potential, given the transmission in blood products. And again, we are just indicating that the U.K.-manufactured Factor XI was used in the U.S. during this period of time.

Quickly moving on, the next component of risk assessment is dose response, again, called hazard characterization. All right, what is dose response? Dose response relates to the amount of agent in a

particular dose to the probability of infection or illness. If you look at this simple dose response model, what I have is a linear relationship, and the power of dose response models is that you can, on the X axis we have this probability of infection - or, I'm sorry, along the Y axis we have this probability of infection, and along the X axis at the bottom we have this quantity of agent. So, if we had a quantity of agent, say, two organisms, that would be associated with the 50 percent probability in this case of infection.

And then, we can use this to link dose that we get from exposure assessment. So, if we knew that our exposure assessment said we were exposed to two organisms, using this dose response we could say, well, that person that's exposed to two organisms has a 50 percent chance of infection.

Now, the issues for TSEs, and the challenges that we face, is that dose response is very unclear for TSEs. First of all, human data are absent. I think we've had some conversations about that already and discussions, and I think people recognize some of the limitations that we have.

Human data is absent. Again, one of the most important things, I think one of the Committee

members mentioned, was that we really need to get a handle on the quantity of agent in human blood or plasma. We know there's possibly variation in the amounts, maybe people have early on - don't have the agent in the blood early on, but as infection progresses, perhaps, the agent appears in the blood. The question for us also, is it present throughout the entire incubation period or are there sporadic occurrences in appearances of this agent in blood?

We also are thinking about genetics and susceptibility of humans, an important factor, is there a threshold or not for this agent? Do you need 100 ID50s, animal ID50s, to become infected, or do you only need one? So, we don't really know that, and we don't know if you get exposed to fractions of infectivity of an ID50 what does that particularly mean as far as infection and a threshold?

And, another issue for us is, is there a cumulation of the agent in humans? We certainly don't know that that occurs at this moment in time.

What we do have is, is we have some animal data available to us, and we do use this in our risk assessment. The question for us is, though, does this animal data that I'm going to talk about approximate the human situation as well as we'd like, and we don't

know that until we have a comparison in the human to make any assumptions about this. Our current assumption in the models is that the animal data is comparable and reflects the human situation on a one-to-one comparison.

The next thing I'm going to talk about, this is more of a clarification, since this term is going to come up constantly, I'm going to use this term, ID50, all the time. ID50 is a commonly used terminology, and it's sort of a metric or the currency that we talk about in TSE risk assessment. So, one ID50 we defined as a dose necessary to initiate infection in 50 percent of the exposed population, and I think it's important to sort of qualify what this term actually means. The inferences are based on animal TSE data, so any ID50 that I talk about is really, you can just put animal ID50 in front of that, because that's what we are actually looking at.

Extrapolation of animal data, that the human outcomes is highly uncertain. Assumptions in risk assessment, again, I just mentioned this, animal data approximate infection and illness in humans at the same rate. We don't know actually if that assumption is accurate or not.

And, I think an important thing to

consider, too, is that exposure, if you are exposed to this agent that may not necessarily lead to infection, and then if you are infected with this organism - I'm saying for saying organism, but with the prion, infection may not necessarily lead to illness. So, I think that's an important issue, too, that we'll talk about in some of the prevalence studies, because there may be a number of infections that may never progress to full-blown illness, and those may not be captured in some of the estimates of prevalence that are currently being used by other researchers and risk assessors.

Just to sort of summarize this whole dose response issue for us, dose response, we believe, provides a useful link in estimating risk based on exposure. I think it's safe to say that dose response at this time is really lacking for TSEs, or at least you can say is highly uncertain. We can use the ID50 as a guide for us, but I think we have to have all the caveats, but that is really an animal system measure that we are using and applying to the human system. So again, there's going to be that big sort of gorilla in the room, which is uncertainty about this estimate.

So again, therefore, predicting probability of variant CJD for humans is extremely

uncertain. I'm going to keep on sort of saying that time after time.

Okay. Now, moving on to the exposure assessment, and I just wanted to say, this is the largest component of our model and of our risk assessment. So, what we are actually doing is we are conducting a model of an exposure assessment, and then we're going to make some conclusions about risk in a moment.

So, what I want you to take home from exposure assessment are sort of two key factors, and those are, in exposure assessment we look at the routes of infection and how a person might become infected or exposed to a particular hazard. We know that, and that's well characterized for Factor XI, people receive that product due to being part of the investigational drug studies in the United States. The other component of that that are really important for exposure are, what's the frequency of exposure or the probability of exposure to the variant CJD agent, and then the second component of this exposure assessment is quantity. So, if we know that a person has been exposed, how much of this particular agent have they been exposed to. That's an important question for us to try to answer.

And, just sort of moving on, this is sort of just a brief outline of the model as I've laid out. So, what we have are three basic components, Parts A, Module A, Module B, Module C, that I'm going to show you in just a second.

Module A, what we are trying to do is, we are trying to predict the probability and the quantity of variant CJD ID50s in a plasma pool. Again, we want to know the probability, and probability not only is related to the possibility that we'll get a positive batch, but it's also related to the amount of agent that you might see. So, I think Doctor Epstein had asked the question that, you may have multiple doses, perhaps, or multiple donations from several variant CJD donors in a particular pool, if the prevalence of the disease is high enough in the population, or the infection is high enough. So, I think that's something very important to consider.

So, probability begins to - as prevalence begins to move up, you are going to see more of this affecting the quantity of agent that's actually in the starting pool.

All right. And then, I think another important aspect that we carefully consider is reduction going on during manufacture, so I'm going to

talk more about that in a moment, and then dose per surgery. This is actually how much of the dose of the product do they receive, and then how much dose of the agent do they actually receive, of the variant CJD agent. So, the quantity of variant CJD in the final product, and then we consider the amount of product actually used by patients.

So, here's sort of a cartoon version, again, of our Factor XI risk assessment, so I've indicated this as part of our assessment in orange, and if you go through this what I wanted people to sort of get out of this is that we have these inputs going into the model, we have probability of variant CJD in the United Kingdom, number of donations, et cetera, and we have it going through a number of calculations, and then we have outputs for each section. Those outputs feed directly next into the next section, and then so on an so forth. So, what we've got are these three major modules that I just described, and ultimately what we are getting out of this is, we are getting the exposure to variant CJD IV ID50s, we are doing that by vial per unit of Factor X, and then for three specific scenarios that patients might encounter as they are being treated with this product.

So, that's sort of the quick overview.

All right. So, this is probably one of the most difficult things for us to calculate, so Module A, the variant - the probability and quantity of variant CJD ID50 in a plasma pool. There's a high degree of uncertainty with these estimates, so I'm going to explain to you two approaches, and there's sort of a disparity in the literature as to the estimates that are coming off each approach, and I'm going to talk about those in just a second.

Again, what we are trying to do is calculate this probability that ID50s will be in the pool or product, and that's directly related to this estimate of prevalence. So, it's important to sort of get this estimate of prevalence as accurately as possible, although a lot of uncertainty again, and what we are doing is looking at the estimation of prevalence of variant CJD in the U.K. population for this particular model.

All right. So, what we did was, we considered the various estimates going about in the literature for mathematical models, and there are several. So, there's Ghani, and I think one thing I should sort of delineate is that these models are sort of linked to the actual cases that are being observed.

So, what you'll see is that early on the estimates were extremely high, 236,000, but as we've seen in the last three years the actual number of cases that started to decrease, what we are seeing is people's estimates of the number of symptomatic cases are also going down.

So, if you look at Ghani's estimates from 2000 to 2003, we go from 70,000 to 236,000, he has several estimates in his paper, this is one of the most extreme estimates, and that correlates to about as low as one in 500 possible cases incubating in the population to about one in 800,000.

Okay. So, as you get up more and more into the more recent data, those numbers are going down. He's estimating a median of about 100 cases and that works out to about one in 500,000 in the population.

And then another paper, Llewyn estimated the possible number of infections incubating in the population at one in 15,000 to one in 30,000.

And, I think one thing that I should say about these models that's very important is, these models are predicting the number of clinical cases that are expected to arise in the future, and what they don't capture is the number of non-clinical, or