FOOD AND DRUG AMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Advisory Committee on

Transmissible Spongiform Encephalopathies

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P R O C E E D I N G S (8:58 a.m.)

Agenda Item: Opening Remarks

DR. HOGAN: Welcome, everybody. I'm glad to see you all made it here today.

The debt ceiling has passed, so that means we could actually meet. To put it in perspective, my 18-year-old son said to me yesterday, "Dad, if they don't pass the debt ceiling, does that mean you have to pay for it yourself?"

The answer, I guess, is yes.

LCDR EMERY: Welcome. My name is Bryan Emery. I'm the DFO for this meeting. I would like to welcome everybody to the TSEAC Advisory Committee meeting today.

I'm going to have everybody on the panel introduce themselves. We have several new members on the panel. We'll start with that.

My name is Bryan Emery, as I said, and I'm the DFO on this committee.

DR. HOLLINGER: I'm Blaine Hollinger. I'm one of the temporary voting members and the chairman of the Blood Products Advisory Committee for the FDA.

DR. HORNICEK: Fran Hornicek. I'm past president of the AATB.

DR. BOSQUE: Pat Bosque. I'm a neurologist in Denver, on the faculty of the University of Colorado.

DR. APPLEBY: Brian Appleby. I'm a neuropsychiatrist at Cleveland Clinic.

DR. MONROE: Steve Monroe, CDC, Atlanta.

DR. KUZMA: Jennifer Kuzma, Humphrey School of Public Affairs at the University of Minnesota.

DR. PRIOLA: Sue Priola, Rocky Mountain Laboratories, NIH.

DR. SALMAN: Mo Salman, Colorado State University, professor of veterinary epidemiology.

DR. HOGAN: Nick Hogan. I do ophthalmology and eye pathology at the University of Texas Southwestern in Dallas.

DR. RENTAS: Frank Rentas, Armed Services Blood Program.

DR. PARISI: I'm Joseph Parisi, neuropathology at the Mayo Clinic in Rochester, Minnesota.

DR. DETWILER: Linda Detwiler, Mississippi State University, College of Veterinary Medicine.

DR. KREINDEL: Silvia Kreindel, APHIS, Veterinary Services.

MS. BAKER: Judith Baker, based at UCLA, the Federal Hemophilia Treatment Centers in Region IX.

MS. HAMILTON: Janice Hamilton, retired from Hemophilia Federation of America, consumer advocate. I still work with them as a consumer advocate. I have been

active in hemophilia for at least 40 years.

DR. BARRAJ: Leila Barraj. I'm a statistician with a consulting firm in Washington, DC.

DR. LEE: Douglas Lee, Grifols, Incorporated.

DR. HOGAN: Thank you.

I think without further delay, we'll go ahead with Topic I. Dr. David Asher is going to talk to us relative to the donor deferral for time spent in Saudi Arabia to reduce risk of variant CJD by blood and blood products and human cells, tissues, and cellular and tissue-based products, with an introduction to the topic and background.

LCDR EMERY: Before we get started, I'm going to read the conflict-of-interest disclosure statement.

The Food and Drug Administration is convening the August 1, 2011 meeting of the Transmissible Spongiform Encephalopathies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from the agencies and are subject to the federal conflict-of-interest laws and regulations. The following information on the status of the advisory committee's compliance with federal ethics and conflict-of-interest laws, including but not limited to 18 USC 208 and

712 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants at this meeting and to the public: FDA has determined that all members of the advisory committee are in compliance with the federal ethics and conflict-of-interest laws. Under 18 USC 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's outweighs his or her potential financial conflicts of interest. Under 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee their essential expertise.

Related to the decision of this meeting, members and consultants of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 USC 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties, and also primary employment.

For Topic I, the committee will discuss donor

deferral for time spent in Saudi Arabia to reduce the risk for variant Creutzfeldt-Jakob disease by blood and blood products in human cells, tissues, and cellular and tissue-based products. This is a particular matter of general applicability. Based on the agenda and all financial interests reported by members and consultants, no conflict-of-interest waivers were issued under 18 USC 208(b)(3) and 712 of the Food, Drug, and Cosmetic Act.

Dr. Douglas Lee is serving as the industry representative, acting on behalf of all related industry. Dr. Lee is employed by Grifols, Inc. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals are not screened by the FDA for conflicts of interests.

This conflict-of-interest statement will be available for review at the registration table.

We would like to remind members, consultants, and

participants that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from the discussions, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that you may have with the sponsor, its product, and, if known, its direct competitors.

Thank you.

DR. HOGAN: Dr. Asher.

Agenda Item: Topic I: Donor Deferral for Time Spent in Saudi Arabia to Reduce Risk of vCJD by Blood and Blood Products and Human Cells, Tissues, and Cellular and Tissue-Based Products

Introduction to the Topic and Background

DR. ASHER: Thank you, Nick. I would like to thank the members of the committee and the public for joining us today for consideration of donor deferral/ineligibility for time spent in Saudi Arabia to reduce the risk of variant Creutzfeldt-Jakob disease transmitted by blood, blood products, and by human cells, tissues, and cellular and tissue-based products. For obvious reasons, I will now refer to the last as “HCT/Ps” for the balance of the talk.

First a couple of housekeeping issues. Everything of importance that I'm going to say is in the issue summary that you have or should pick up from the front desk. There is a small error in the issue summary that will be corrected when it goes on the Web. In the second paragraph, the case that Mike Coulthart is going to be presenting to you later this morning became ill in 2010, not early in 2011.

The issue being presented today has involved an unusually large number of FDA employees. I won't list them in the talk, but you can see them listed here in the acknowledgments. Furthermore, two temporary voting members of the committee with us today, Frank Rentas and Mo Salman, have been very helpful in the run-up to today's meeting. We are particularly grateful to Mo Salman, who is probably the only person on the committee who is not only an expert in animal population health, but has actually been in Saudi Arabia in a professional capacity several times. Thank you very much for joining us today, Mo.

We are very grateful to our invited speakers: Bob Will, professor, neurologist, epidemiologist, founder of the UK CJD Surveillance Unit and a leader in world surveillance; Mike Coulthart, coming to us from Canada to present the case diagnosed there earlier this year; Larry Schonberger, who will present two cases diagnosed in the

United States; Lieutenant Colonel David Lincoln, who will be describing the potential impact of deferrals on the military blood program.

Finally, we would like to express our gratitude to the staff of the Food and Drug Authority of the Kingdom of Saudi Arabia, who have been helpful and we hope will continue to be helpful as we address these issues. I understand that they may have a statement that they will present or have presented during the open public hearing.

Thanks to you all.

First, a matter of terminology. Unsuitable blood donors, plasma donors are deferred. Unsuitable donors of HCT/Ps are found to be ineligible. I'm in the Office of Blood and will probably mainly use the term "deferred." But please understand that when I use it, it covers ineligible tissue donors as well.

I'm going to go over today's issue, give you a little refresher background on variant CJD and blood safety and, by implication, HCT/P safety, discuss briefly variant Creutzfeldt-Jakob disease in three long-time residents of Saudi Arabia, and then address potential dietary exposure to the agent in Saudi Arabia, our considerations for possible additional deferrals, ineligibility for donors resident in Saudi Arabia, the potential impact of deferrals on the supply of blood donors and, by implication, on

eligible HCT/P donors, and briefly compare Canadian deferrals for blood donors resident in Saudi Arabia with those of the Food and Drug Administration, and then the first reading of the questions.

Many of the points that I will discuss in brief will be explained in greater detail by later speakers.

We seek advice from the committee on whether, based on the recognition of three cases of variant CJD in individuals likely to have been infected with the BSE agent in Saudi Arabia, to modify current vCJD-related safety recommendations. We are deferring certain blood and plasma donors or finding certain donors of HCT/P ineligible to donate because of time they spent in Saudi Arabia.

Variant Creutzfeldt-Jakob disease shares the general properties of other spongiform encephalopathies -- most striking, spongiform changes in the cerebral cortex -- but it has a unique set of features as well: different age of onset, different presenting signs and symptoms, different cerebral imaging, and somewhat different neuropathology, florid plaques in the cerebral cortex and accumulations of prion protein in lymphoid tissue.

Variant Creutzfeldt-Jakob disease, a human infection with the BSE agent, is unique in being the only zoonosis -- that is, an animal TSE accidentally spread to humans. Most vCJD infections, we believe, are foodborne,

but five infections in the United Kingdom have been attributed to blood products. We look forward to hearing from Bob Will some more about surveillance of recipients of blood products in the United Kingdom.

Unfortunately, there is only one effective risk-reduction strategy that's available for blood components and HCT/Ps, and that is to reduce the number of donors who have been an increased likelihood of exposure to the BSE agent -- so-called geographic donor deferral or ineligibility criteria. Donor testing is under study, but is not yet available, and reliable infectivity removal techniques for blood components -- some promising reports, but not available on the market. Plasma derivatives do undergo effective agent-removal steps.

Geographic donor deferrals reduce the risk, but they are nonspecific and highly inefficient, in that we believe that most of the deferred donors are not, in fact, infected with the BSE agent. If otherwise suitable, it means that we are losing a significant number of valuable blood donors because of these policies. But it's the only method available to reduce the risk.

Donor deferral recommendations are also not fully effective. There is no reason to think that an occasional donor couldn't get exposed and infected with the BSE agent during a short time in a high-risk BSE country. If you

look at the current policies, you will see that they are not internally completely consistent one with the other.

When persons in new countries are recognized to pose a potential VCJD risk, FDA believes it prudent to consider modifying our FDA geographic BSE-related recommendations for donor suitability/eligibility, and that's what we are doing today.

Just to repeat, there have been four recognized transfusion-transmitted infections, three of them clinical cases. It's nice to see that the last reported case we are aware of occurred in 2007, none since. Perhaps Bob Will will share with us his thoughts for why we have seen no cases after that. Then in 2009, a case was attributed to use of human plasma-derived factor VIII. So far as I know, no cases attributed to treatment with that product, which was never licensed in the United States -- no cases since.

Most of the cases, as I mentioned, are thought to be foodborne in persons with the most common genotype of the prion protein-encoding gene -- that's methionine homozygous at codon 129 -- about 40 percent of the normal UK population. The incubation period median appears to be about 12 to 13 years. One doesn't know -- there have now been three or four probable infections and one clinical case in persons with other genotypes, and just judging by when the first cases were recognized, it's possible to

predict a median incubation period that might be as long as 32 years. For both groups of patients, we anticipate, if they are like other spongiform encephalopathies, that some patients could have incubation periods exceeding 40 years, as has been seen with Creutzfeldt-Jakob disease -- for Creutzfeldt-Jakob disease, 38.5 years, and over 40 years for kuru.

Transfusion-transmitted variant CJD has had shorter incubations periods, anywhere from 6 to 8.5 years. The plasma-associated case -- you can’t identify point exposure the way you can with a blood component, but it’s possible that it’s about 11 years, or similar to dietary cases.

The differences between transfusion-transmitted Creutzfeldt-Jakob disease and other Creutzfeldt-Jakob disease cases are very striking. There have already been, in four cases out of a relatively small number of people at risk for variant Creutzfeldt-Jakob disease -- and no cases attributed to transfusions from donors who ultimately came down with Creutzfeldt-Jakob disease, with sporadic Creutzfeldt-Jakob disease. So transfusion-transmitted variant Creutzfeldt-Jakob disease is considered definite, while that from other forms of Creutzfeldt-Jakob disease is only a theoretical possibility. How long before onset of clinical vCJD is blood infectious? We know from one of the

donors that transmitted disease 3.5 years before becoming ill that the period of infectivity in the blood can be certainly that long, and we don’t know how much longer. We don’t know whether the same thing is true of -- all these donors were 129 methionine homozygous, and we don’t know whether the amounts of infectivity in blood of people with other genotypes, long incubation periods -- we don’t know whether the levels of infectivity are similar or for how long they are infectious, if they are.

Variant CJD has now been attributed to residents in Saudi Arabia. All three of them have had the more common PRNP genotype. They have had no history of transfusion or significant surgery, so they are presumably foodborne infections. The dates of residence in Saudi Arabia for all three cases encompass plausible variant Creutzfeldt-Jakob disease foodborne incubation periods. Other countries are less likely places where infection might have been acquired, though that is not impossible. No case has been convincingly attributed to residence in any other country of the region, and both US and Canadian authorities have concluded that the infections were most likely acquired in Saudi Arabia.

Important to note is that before they became clinically ill, all three of the Saudi-associated vCJD cases were in people who would have been considered

suitable/eligible to donate blood and HCT/Ps according to our current recommendations. There have been three other cases recognized in North America. All three of those were in former UK residents, and they would have been deferred/found ineligible.

We have been attempting to estimate the magnitude of the possible risk of dietary exposure to BSE agents in Saudi Arabia. Now I would like to share our thinking with you.

The UK probably exported to Saudi Arabia products potentially contaminated with the BSE agent during the generally accepted UK BSE-highest-risk period, which begins in 1980, the presumptive beginning of the BSE epidemic in the UK, through the end of 1996, when a full range of food-chain and animal feed-chain protections had been implemented in the United Kingdom and when the European Commission prohibited further exports of bovine-related materials from Saudi Arabia to third countries. Those exports included live cattle, beef products, and rendered protein, meat-and-bone meal. Saudi Arabia has not recognized BSE in its own cattle, although BSE has rarely been recognized in two other countries in the region. Oman imported two cows found to have BSE from the UK in 1989, and Israel recognized one case in a native cow in 2002.

There are a number of uncertain risks that might

be relevant, but we have been unable to assess their likelihood. The UK might have exported significant amounts of contaminated materials to other countries in the region. There have probably been exports to the region from other BSE countries. There is presumably some cross-border trade in the region. There is a theoretical risk that indigenous BSE might have been established in cattle in Saudi Arabia, although the numbers of cattle there are relatively small compared with European countries. There is even a remote possibility that other ruminants might have been infected, although that has not happened in the UK, where an occasional case has been attributed in goats or sheep to infection, but it has not become a problem. Those are all due to rendering practices and the feeding of meat-and-bone meal to ruminants. Of that, we have no information regarding Saudi Arabia.

So this is the information that we have been able to consider. One, we looked at the crude rates of recognized variant Creutzfeldt-Jakob disease from 1996, when the first cases were published by Bob Will and colleagues, to the present time that have been attributed to time spent in various countries. We looked at records of bovine-related exports to Saudi Arabia, estimated fraction of UK beef that was used in Saudi Arabia, and the overall beef consumption in Saudi Arabia. We have received

some anecdotal information to suggest that our estimates may be too conservative, but we really don’t know how to deal with that. This caveat must be kept in mind throughout: The information available to us is limited, quite uncertain, mostly unverified, and the reliability of some sources cannot be estimated. For instance, there are commercial websites that give useful information, but the source of the information is from, quote, anonymous highly trusted authorities, and we simply can’t verify how well informed those authorities are.

But we can be confident in at least the crude rate of vCJD compared to the reported population of the countries involved. What I show here are the cases that are attributed to infection in a country divided by the most recent US Census Bureau estimates for the total population of that country. We accepted the CJD Surveillance Unit convention of attributing cases resident in the United Kingdom for more than 6 months to infection in the United Kingdom. We cannot correct, for most of the countries, the population for its age distribution, which is important because, as you know, there is a predilection of variant CJD for younger people, and for the efficiency of case recognition, not just for Saudi Arabia, but for some of the European countries. So keep that in mind. These are crude figures.

In 2002, Moira Ricketts, who was then working for the World Health Organization -- she is now, I believe, with the Canadian Medical Association -- presented to this committee her analysis of UK customs and excise data for exports of bovine products from the United Kingdom. Shown here are the figures that she came up with for exports of live cattle from Saudi Arabia. You can see that they imported somewhere between 100 and 1,000 cows between 1980 and 1995. But they are not the only ones who imported a significant number of cattle. You can see in black a number of countries, including countries in Southeast Asia, that imported more than they did, including Brazil, Argentina, Australia, and New Zealand, which have seen no cases of BSE at all. But Saudi Arabia did import, according to excise records, cattle from Saudi Arabia (sic).

Saudi Arabia also imported carcass meat between 1980 and 1996 -- as you can see, here over 1,000 metric tons. But they are not the only country that did it, and some of the countries have not seen either variant CJD or BSE.

Finally, meat-and-bone meal: Saudi Arabia imported a reasonable amount of meat-and-bone meal during the years of concern, but there are other countries that have imported more and have not seen cases of either BSE or

variant Creutzfeldt-Jakob disease.

Sanchez-Juan, with Bob Will and other colleagues, did an interesting analysis that they published in 2007, attempting to correlate imports into various countries with their later recognition of variant Creutzfeldt-Jakob disease. At that time they were aware of only one case in Saudi Arabia. You can see that they imported more cattle than did a number of countries that had not seen any variant CJD, but not as much as some other countries, seen towards the right of the slide here. There are live cattle on the bottom and the number of vCJD cases on the left.

The correlation was somewhat better with imports of meat from the United Kingdom. You will notice that the imports in Saudi Arabia fall somewhere in the region of imports into Portugal and Spain.

Moira Ricketts listed the following uncertainties or limitations about UK customs and excise data, and I suspect that the same is true for the interpretation published by Sanchez-Juan:

· The information is not informative about bovine exports from countries besides the UK.

· The export data did not tally with national import records. That is, some of the countries had no record that they had received material that UK said had been exported.

· There was no information about repackaging, onward sales, which probably explains why they didn’t have any record of receiving it. Those practices possibly obscure UK origin of products.

· Illegal or uncontrolled shipments -- that is, somebody buys meat in one country and carries it across the border into another country -- are not accounted for.

· There was no information about actual use of, for instance, meat-and-bone meal, which is high-risk in animal feeds and lower-risk when it’s used for field fertilizers.

So we are left, really, with the observation that the prevalence of variant CJD in the Saudi population is not dissimilar from those in a number of other countries, about the same as that in Spain, a little less than that in Portugal and the Netherlands, and substantially less than the prevalence in the UK and France.

Since the overall vCJD prevalence is not greatly different from rates for several European countries, we conclude that the overall risk for dietary exposure to the agent by the Saudi population as a whole was less than that in the UK, but not dissimilar from that in some other European countries. Since 1999, we have tried to use a simple model to estimate the risk of dietary exposure to the BSE agent in various countries, by taking their risk as

a percentage of the UK risk, as 100 percent. After 1996, as I have mentioned, we consider the risk in the United Kingdom to have become negligible. We adjust our recommended geographic deferrals, allowing a certain margin of safety, to consider the risk relative to that in the United Kingdom. Again, this information is highly uncertain.

The risk we are really concerned about is the eating of UK beef. But we have found that dietary history of donors is not reliable -- I won't go into the underlying data -- so as a proxy for beef consumption, we use the time that a donor spent in a BSE-risk country. The assumption is that risk is random and directly related to the time spent in the country of concern. The longer you spend, the more chances you have of eating a contaminated beef product. We estimate that relative to UK during those years taken to be 1, the risk in France was about 5 percent, which is to say that 20 days spent in France, we estimate, is equivalent to 1 day spent in the United Kingdom during the risk period; Switzerland, 1.5 percent, or about 60 days equivalent to 1 day in the United Kingdom; other European countries for which we had no figures as being equivalent to Switzerland. For military bases in Europe during the years when they were buying beef from the United Kingdom, we estimate the risk to have been about 35

percent of that in the United Kingdom.

What might a reasonable exposure risk estimate be for Saudi Arabia? We considered four populations of concern, 1980 to 1996 (again, we consider risk from UK to be negligible after that time):

· US active-duty military. Very few dependents of the military lived in Saudi Arabia.

· Military contract workers and their dependents.

· Non-military contract workers and their dependents.

· Finally, Saudi nationals.

I might point out here that the main difference between military and other contract workers is that military contract workers tended to have relatively short periods of residence, a couple of years or less, whereas non-military contract workers, many of them, stayed for more than 5 years.

For the US military, we assume that the risk of dietary exposure on Saudi bases during the years of concern might have been similar to the risk on US military bases in Europe south of the Alps. The DOD has estimated that the actual procurements of beef from the UK during those years might have been somewhat less than on European bases, perhaps as little as 10 percent. But as a safe worst-case assumption, we are assuming that Saudi bases are similar to

bases in Europe.

We currently recommend deferral for blood donors and other donors who spent six months or more on bases south of the Alps from 1980 to 1996. We are considering recommending similar criteria for donors who served on US bases in Saudi Arabia from 1980 through 1996.

For contractors, we assume that the BSE exposure risk of all contractors is similar to that for the general Saudi population, because they all purchased food from local non-US military establishments. The military did not provide, we are told, meat to contract employees. There is a caveat here, and that is that both the diets and the medical care of contractors, military and non-military, might not have been the same as that of the general Saudi population. It’s possible that they ate more beef and it’s possible that they ate more UK beef than did the general population. It’s also possible that they have a greater likelihood of being diagnosed with CJD if they become ill.

The dietary risk of BSE exposure by Saudi nationals we estimate was probably much lower than the risk for the general Saudi population. UK export and Saudi import records suggest that only about 10 percent of Saudi beef was imported from the United Kingdom and the USDA figures suggest that the average per-capita estimated beef consumption in Saudi Arabia is only about 25 percent of

that in the United Kingdom -- in Saudi Arabia lamb and chicken are much more popular than beef -- which yields a total estimated Saudi potential dietary risk of about 2.5 percent of that in the United Kingdom. So we're assuming that the risk of dietary exposure to UK beef by contract workers and Saudi nationals was similar to the risk in non-UK Western European countries during the years 1980 to 1996. The non-UK countries in Europe with the highest risk are France and Ireland, and it seemed that a prudent assumption might be that the risk in Saudi Arabia is unlikely to have exceeded the risk in France. So we assume that the BSE exposure risk in -- we, however, assume that the BSE exposure risk in Saudi Arabia, unlike France, which has had BSE established in its native cattle, is attributable almost entirely to imports of UK beef products, and that risk became negligible after the end of 1996.

We currently recommend deferral for donors who spent more than 5 years in France, as well as donors with a history of transfusion in France, from 1980 to the present time. We are considering recommending suitability criteria for any donor of the products we are considering who spent a cumulative 5 years or longer in Saudi Arabia during the years 1980 to 1996, which is similar to the current recommendations for residents of France, but not extending

to the present time and not including a deferral for history of transfusion.

Canadian blood establishments now defer any donors who were residents of Saudi Arabia for any aggregate period, six months or longer, from 1980 to the end of 1996. Our policies and Canadian policies are somewhat similar, although they are not identical. That's largely because the implications of donor deferrals, especially for former military, are different for Canada and the United States.

In the handout you have a comparison of US and Canadian deferrals. I point out that Canada is not uniform in its deferrals. Héma-Québec and Canadian Blood Services have different deferral policies. Perhaps Mike Coulthart will comment on that. I won't go through these columns, in the interest of time. I will point out that we recommend deferral of personnel resident on US military bases in Europe north of the Alps through 1990 and south of the Alps through 1996, when the imports of beef from the United Kingdom end.

Finally, Hong Yang will be presenting for you later in the morning the estimated losses that we might expect if we recommended the two policies that we have been discussing. The most likely estimate was that we would lose about 21,000 former military. They are almost all now in the civilian blood program. We wouldn't lose any donors

who were military contractors because their contracts were so much shorter. We might lose something over 2,300 non-military contractors, a few Saudi immigrants to the United States, for a total of fewer than 25,000 donors, or about 42,000 donors a year, which is about two-tenths of 1 percent of our current estimated blood donor population.

In conclusion, there have been three cases of variant Creutzfeldt-Jakob disease now attributed to dietary exposures in Saudi Arabia. Those donors would have been suitable donors. The crude prevalence in Saudi Arabia is not markedly less than those in several European countries. The most likely source of dietary exposure, we reckon, was imported UK beef. Those exports ceased by the end of 1996. We acknowledge a theoretical possibility that Saudi Arabia might have imported contaminated products from other countries after 1996 or introduced BSE into their own cattle herds, but those seem less likely sources of exposure.

The US military procured an unknown but possibly significant amount of beef from the UK in those years. We consider a plausible worst-case assumption that the amount of beef consumed by US military might have been similar to that on bases south of the Alps, 1980 through 1996. We assigned a risk factor of 35 percent to the southern military bases, and so we propose the same risk estimate

for the Saudi bases through the end of 1996. We are considering a recommendation to defer those donors for any 6 months or more spent on the bases during those years.

At least 10 percent of beef consumed by Saudi nationals might have been imported from the UK, but their total beef consumption appears to be much less than that in the UK. We have tentatively assigned to Saudi Arabia a risk of 2.5 percent of that in the United Kingdom through the end of 1996. We consider that contractors bought beef products in the same establishments as did Saudi nationals, so they have the same risk.

Considering the current estimates of crude prevalence in Saudi Arabia compared with Europe, it seems prudent to assume, as a realistic worst case, that the true prevalence in Saudi Arabia is unlikely to exceed that in France. We believe that the opportunities for dietary exposure to the agent in Saudi Arabia, unlike France, became negligible after the end of 1996.

We currently recommend deferral/ineligibility for all donors who spent more than 5 years in France from 1980 to the present, and we are considering a similar recommendation for donors who spent a cumulative period of 5 years or longer in Saudi Arabia.

We estimate that the number of additional otherwise suitable donors who would be deferred under the

new recommendations would be relatively small, perhaps two-tenths of a percent of the current donors.

So the questions for the committee to consider today:

Do the available data support the consideration by FDA to recommend deferring donors of blood and blood components, including source plasma, and to determine to be ineligible donors of HCT/Ps who spent six months or more cumulatively in Saudi Arabia as US military personnel from the beginning of 1980 through the end of 1996 or otherwise spent more than 5 years cumulatively in Saudi Arabia from the beginning of 1980 through the end of 1996?

Furthermore, we request that you discuss the likely contribution of the recommendations both to the safety of the products involved and the possible impact on supplies of blood, blood components, plasma derivatives, and HCT/Ps, and to comment on additional information that might better inform our consideration of the proposed or any future safety measures.

Thank you.

At this point I think it’s time to hear an update on vCJD in the United Kingdom and worldwide.

DR. HOGAN: Are there any quick questions for Dr. Asher, before Dr. Will comes on?

(No response)

Thank you very much.

We are very lucky to have Dr. Robert Will with us this morning to give us an update on the world situation. As you know, Dr. Will is one of the most eminent prion TSE experts in the world. We are glad to see you again.

Agenda Item: vCJD World Situation and Updates

DR. WILL: I'm very grateful to be here, and I'm very grateful for the invitation to come again to speak at one of these meetings.

As I have said before, it is always very difficult to follow David Asher, because he gives such a very clear description of what's happening. I will just try and fill in some of the details in my presentation.

I have been asked to talk about the world situation with variant CJD and give an update.

This is a slide I have shown before. This shows the situation in Europe with variant CJD and BSE. It's an important slide because it shows that variant CJD and BSE are both in clear decline. There is a hope that the BSE epidemic will eventually disappear. With variant CJD in the UK, there is also a decline from a peak in deaths in 2000. But as you will see, there is a long tail here, with one death so far in 2011. As Dr. Asher said, there is a possibility that this tail could go on for an extended period.

The question of further outbreaks of variant CJD due to primary transmission, presumably through dietary exposure, is important in relation to the genotype of the affected individuals. To date, all the definite and probable cases of variant CJD in the UK have been methionine homozygotes. That is still the case. Some of the cases weren't tested, and there is one individual who is a possible case of variant CJD who was a heterozygote. But that case was described about a year ago, and we have had no further heterozygote or valine homozygote cases.

Importantly, the variant CJD cases worldwide, outside the UK -- all of those have been tested and all are methionine homozygotes.

There is a concern that we may see further outbreaks at a later date in the alternative genotypes, but most people think that it is unlikely that, if that should occur, those outbreaks will be bigger than the primary outbreak.

What is the incubation period of variant CJD? Well, of course, we don't know. There are many uncertainties about variant CJD, which I will come to as we go through this presentation. One way of looking at this is to look at the cases that are thought to have been exposed to BSE in the UK and then developed the condition when they returned to their country of origin. This is the

list here. It's a pretty difficult slide to explain. We presume that in 1996 human exposure to the BSE agent stopped in the UK. If you look at the periods of residence of these individuals and take a mean of when they were likely to have been exposed in the UK, you can see that the figures are remarkably consistent -- 15 years, 30 years, 16 years, 16 years, 17 years, 14 years for the French case. The Irish case is the one with the shortest potential incubation period. But, of course, there is the possibility that this case was exposed in Ireland and not the UK.

This is very consistent with an analysis done by Larry Schonberger and Ermias Belay some years ago suggesting that the mean incubation period may be around 15 years. This is consistent with mathematical models carried out by various groups, particularly in France.

Of course, there will be a spread around this mean. We simply do not know what the maximum incubation period will be or the minimum incubation period.

Now I'll turn to the TMER study. This is a study looking at transmission of variant CJD through blood transfusion. As I have told you before, this is a simple study -- a simple-sounding study, at least -- in which every case of variant CJD that is identified in the UK -- the details are circulated to the blood authorities in the

various parts of the UK and a search is made as to whether they had been blood donors. If they had been blood donors, a search is then made to find out whether the blood was actually used, and if it was used, who the recipients were. The idea of this study is to determine whether any of the recipients of blood donated by individuals who subsequently developed variant CJD themselves developed variant CJD, suggesting a potential causal link.

These numbers have changed little over many years. I, not recently, had a case of variant CJD who had been a blood donor. There has been a change. This used to be 66, but it is now 67, because someone who was carefully looking through some records found an additional recipient of a platelet transfusion.

This shows the data that David Asher explained to you. These are the individuals who are known to have received blood transfusion from an individual who subsequently developed variant CJD. Each dot represents one individual. This is shown according to recipient survival to death and the time from donation to clinical onset in the donor, in years. You can see that we have three clinical cases of variant CJD which are thought to be linked to blood transfusion. These individuals developed variant CJD clinically between 6 and 8.5 years after the blood transfusion. We have one case that was positive in

the spleen, although this individual died of an intercurrent illness and had no evidence of variant CJD in the brain. This case specifically underwent necropsy because of the knowledge that they had received the blood transfusion, and a search was made through their tissues to find out whether there was any evidence of infectivity. Infectivity was found in spleen.

In terms of the timing of the donation to onset of clinical symptoms, this gives you some idea of when infectivity is present in blood in individuals who are going to get variant CJD prior to clinical onset. As you can see, between 1 and 3.5 years, these individuals must have infectivity in blood before they develop the clinical symptoms.

So this clearly shows that blood in variant CJD is infectious in the incubation period. But we do not know for what extent of time blood is infectious prior to clinical onset.

This is an update of the individuals who are currently surviving. There are 18 of these individuals who have received a blood transfusion from someone who subsequently developed variant CJD and are currently alive. These symbols are in different colors because after 1999, the cells were leukodepleted, whereas there are individuals like the clinical cases who are still living who received

red cells or whole blood. There are a small number of these individuals who have now survived for at least 12 years after the blood transfusion.

These individuals are clearly at significant risk of developing variant CJD and all have been informed of their risk on more than one occasion and have been asked to participate in research. Some of these individuals have agreed to do so -- for example, by donating blood samples. There are individuals who are currently alive who received whole blood or red cells, who have had a blood donation within a relatively short period of clinical onset in the donor, and the blood may be considered to be likely to have been infected.

An important question is, why is it that these individuals have not developed variant CJD? There are a number of possibilities. It may be that blood is not always infectious prior to clinical onset. It may be that there are specific host factors in these individuals that reduce their risks -- for example, their codon 129 genotype.

Just in brief, the records -- we are very fortunate -- have been relatively complete in all the blood studies that we have looked back at in the TMER. That is, we do know who the recipients were of the blood that was donated. One of the messages here is that record systems

are extremely important. There was one individual who received a blood transfusion many years ago, in infancy, who was presumed to be a case that was due to dietary exposure, but careful investigation revealed that there was a potential shared donor with another individual. I won't go into this in detail. It's very complicated. But basically we have a number of at-risk donors to this individual case. This is thought to be a primary case. One of these at-risk donors may have contributed blood to both these hospitals, but that cannot be confirmed.

What we do know is that this donor, who could have been the source of infection, is still alive. This blood transfusion was given in 1989. So that's the extended survival of this individual, contained infectivity in blood. Statistical analysis has been carried out, and the likelihood is that, in fact, these probably are two primary cases and not cases linked to blood transfusion, although this cannot be excluded.

A lot of work has been done to try and predict the future in relation to variant CJD using mathematical models. One of the teams that have led this is Azra Ghani's team, with Tini Garske. This is a publication in PLoS One which attempts to predict what will happen with variant CJD in the UK in the future.

This is the conclusion, basically. In terms of

the total number of cases, there may be a secondary peak, but this is likely to be relatively small -- that is, 10 cases. However, you will also note the scale along the bottom here. This is between 2000 and 2080. This is over an extremely protracted period of time. The feeling is that some of these cases may be unidentifiable transfusion-associated cases -- that is, individuals how are infected with variant CJD who never develop the clinical illness, but donate blood and individuals who receive the blood and then develop variant CJD. Such cases would not be identifiable through the TMER study. But the numbers, again, are thought to be relatively small.

There are also predictions on the basis of what may happen in heterozygotes and valine homozygotes -- again, the predictions suggesting a very limited clinical outbreak in those genotypes.

But I must stress, this is a mathematical model. It makes lots of assumptions that cannot be validated. But it is at least a measure of what might happen in the future in the UK. Hopefully, variant CJD may not recur as a major epidemic.

One of the figures in this paper is an estimate of the time-dependent exposure of the UK population to the BSE agent through dietary exposure. This shows this gradual increase in potential primary risk related to

dietary exposure, with a sharp cutoff in 1989, when the UK introduced the specified bovine offals ban, which was meant to minimize human exposure to the BSE agent. Of course, this was many years before the identification of variant CJD.

However, that didn't stop all potential exposure. There is this small additional period of exposure between 1990 and 1996, when further measures were introduced to minimize exposure to the human population. This is partially because the SBO ban wasn't fully implemented and because of the possibility that dorsal root ganglia, which were not an SBO, may have continued to enter the food chain that had been derived from cattle that were infected with BSE. But the major risk was clearly before 1990.

This is a plot of all the cases of indigenous variant CJD in the UK by year of birth. There are some older patients with variant CJD. But the important issue is that in the UK there is still no UK-born case born after 1989, when the SBO ban was introduced. This, of course, may change in the future. But, of course, the primary epidemic is clearly in decline, and it raises the possibility that the measures that were introduced to minimize human exposure were at least partially effective.

Blood that was donated from individuals who subsequently developed variant CJD was used for labile

blood transfusion, et cetera. Some units were also sent for plasma fractionation. Here's the total over a period of years from 1986 to 1998, when plasma for the production of plasma products in the UK was imported from other countries, mainly the USA. As you can see, there were a number of units that were used for plasma fractionation, going back to 1986, 1987. It's a matter of significant interest as to whether this resulted in any significant risk to those individuals who were treated with plasma products, including patients with hemophilia.

For that reason, a study was started by James Ironside and colleagues in order to specifically look at individuals with hemophilia who died, to determine whether any of their tissues had evidence of infectivity that might suggest infection with variant CJD. As was discussed at the last meeting, PrP^{res} of the type 2B associated with variant CJD was identified in the spleen of an adult hemophiliac patient in the UK. This raises the possibility that this individual was infected through factor VIII, and not necessarily through dietary exposure. A detailed statistical analysis was again carried out by the Department of Health, by Peter Bennett and colleagues, and their conclusion was that the most likely source of infection -- if this indeed is infection with variant CJD -- was due to previous treatment with factor VIII,

although, as David Asher has suggested, the type of factor VIII that was probably implicated was not in use in the United States.

An important question is, what is the at-risk population of individuals with hemophilia in the UK? Akram Zaman and colleagues at the HPA, in association with the hemophilia doctors' association, have looked at the risk of variant CJD among patients with bleeding disorders known to have received potentially contaminated plasma products, because, of course, we not only know that plasma was donated for plasma fractionation, but we know exactly which lots were contaminated.

This is the conclusion of the study. In terms of hemophilia A, those who were registered who are at risk of vCJD -- that is, treated with UK-sourced plasma products between 1980 and 2001 -- are 2,246. Registered patients at risk who are known to have received implicated clotting factor batches are 556 individuals. But I stress this footnote. Eleven million international units of implicated batches remain unaccounted for. As a result of this under-notification, approximately 50 percent of all patients who had received implicated batches are not included in this analysis. So this is an underestimate of the number of individuals who were exposed.

By looking the treatment regimes of these

individuals, exactly which batches they received, over what sort of periods, they were able to work out the lifetime cumulated vCJD infectivity received by the individuals. Here is the percentage of patients and here is the estimated infectivity exposure, which includes some individuals who received between one and two ID_{50}s and a small number who received greater than two ID_{50}s in the course of their treatment regime.

They conclude that 604 of the 787 patients were followed up for more than 13 years following exposure to an implicated batch. For those 604 patients, the estimated vCJD risk is greater than 50 percent for 164 and 100 percent for 51. This is an underestimate by a factor of 2. Ninety-four, or 16 percent, received implicated batches from donations within 6 months of clinical onset in the donor, raising the potential risk, and 25 percent received their first dose under the age of 10 years, which suggests that they had a period of follow-up that is likely to have been significant.

It does raise an important question: Why are there not more cases of individuals in the UK who have been infected with plasma products?

We have, of course, looked at all the individual cases of clinical variant CJD to determine whether any of them were exposed to plasma products. This is the

conclusion. Not surprisingly, some of these individuals had been exposed to UK-sourced plasma products. Some had been exposed to non-UK-sourced plasma products. In total, nine cases received products on 12 occasions between 1970 and 1998. Of these, five cases received anti-D, four at childbirth; four cases, IM immunoglobulin for travel, thought to be very low-risk products according to the mathematical analysis. One case received albumin. It was a low- to medium-risk product. The batch number was known for four products, and none were from a known vCJD case.

So our conclusion is that, to date, as far as the clinical cases of variant CJD are concerned, we do not think any of them were caused by exposure to plasma products.

Now I'm going to turn to the situation of variant CJD worldwide. This is a table that I think you may have seen before. This is the current situation: UK, 175 cases, three of them clinical cases related to blood transfusion; a small number of cases in other countries, particularly in France, with 25 cases; Saudi Arabia, one case; the USA, three cases, two of which were UK-attributed and one of which was attributed to Saudi Arabia; and most recently, the second case in Canada, which is again attributed to an exposure in Saudi Arabia, which is something of a surprise.

One important question for the European cases is whether these are likely to have been caused by exposure to indigenous BSE, because of these countries have BSE epidemics of their own, or whether they were exposed to UK exports. That is why the study was done by Sanchez-Juan, which has many caveats, as David Asher has explained. There is much confounding in this study. For example, if you look at exports of MBM to particular countries, that may have a direct relationship to the occurrence of indigenous BSE, but it may also correlate with other exports. So it’s very difficult to separate the individual risks.

We felt that the main conclusion of this study was that it was likely in European cases of variant CJD, outside the UK -- the most likely correlation was either with carcass meat imports from the UK or live bovine imports, and not correlations with indigenous BSE. This is, of course, very relevant to the issue of Saudi Arabia.

Just in passing, one important question in variant CJD is, if its risk was due primarily to dietary exposure to the BSE agent, what type of exposure was important? We have always believed that it’s most likely that the relevant exposure was to high-titer infectivity in brain, spinal cord, dorsal root ganglia, et cetera. This is an opinion given by the SSC of the European Union many,

many years ago. This is their table, which summarizes the total infectivity in a BSE case, with the great majority of the infectivity being in the brain, some in spinal cord, about a quarter, and then much lower levels of infectivity in trigeminal ganglia, dorsal root ganglia, and ileum, with very small amounts possibly in spleen and in the eye, although that is hypothetical.

What is not on this chart is beef. But, of course, one of the problems with this is that in the slaughter process it is possible that there is cross-contamination within the abattoir. Also what carcass beef is defined as is not very clear. Does it include components of dorsal root ganglia, for example? So it’s a difficult issue deciding on what the relevant exposure to humans was.

I just return to this table. There have been some changes -- notably, a case of variant CJD identified in Taiwan and also the new case in Canada.

The case of variant CJD in Taiwan was published last year. It’s a probable of variant Creutzfeldt-Jakob disease. The clinical details are provided in the paper:

· This was an individual in the appropriate age group -- variant CJD predominantly affects younger individuals, under the age of 50 -- a 34-year-old individual.

· Duration of illness, which was slightly extended, at 28 months.

· A typical clinical phenotype -- psychiatric onset, pain, ataxia, myoclonus, and dementia.

· Codon 129 MM.

· Pulvinar sign positive on the MRI scan.

· No tonsil biopsy or necropsy.

· A final diagnosis of probable variant CJD.

I think, in relation to discussion about the cases from Saudi Arabia, it’s important to consider what that actually means. We have done an analysis of all the cases of variant CJD in the UK and all referrals. The sensitivity of the diagnostic criteria for variant CJD is over 85 percent, probably over 90 percent if you look at the MRI scan sequences. But the important issue is that to date, every case of variant CJD diagnosed in life as probable that has come to postmortem has had the diagnosis confirmed. So this is highly specific for variant CJD, and it is highly likely that despite the absence of necropsy, this case indeed had variant CJD.

The exposure: BSE is not known to occur in Taiwan. The patient had lived in the UK from 1989 to 1997. The presumed exposure was in the UK.

Of course, the case in Canada is also presumed to have been exposed outside the UK, in Saudi Arabia, as Mike

Coulthart will describe. I'm not going to go into that in detail.

The question that was asked was whether or not there were exports from the UK to Saudi Arabia that might have resulted in an exposure of this individual to BSE infectivity.

This is the latest OIE update of risk of BSE in various countries -- negligible BSE risk in a whole range of countries now. This has recently been extended, including Denmark and Finland. Controlled BSE risk -- a larger number of countries, of course including the UK, the United States, and Canada. Saudi Arabia does not feature on these lists. I suspect that has not been formally assessed. But as far as I'm aware, there are no reports of BSE in Saudi cattle. Therefore, any human exposure to BSE is most likely to have come from imports from outside Saudi Arabia, potentially from Europe, particularly from the UK.

I'm going to show you some data which is based on UK customs and excise information that was supplied many years ago to Moira Ricketts and some other people by what was then the Ministry of Agriculture, Fisheries, and Foods. This is data that has not been validated by the importing countries. One or two countries have tried to validate it in relation to what was stated to have been imported, notably France, who did validate the figures, more or less.

Therefore, this is soft information, and there are major caveats to it.

I'm going to show a much better table in a minute. This is UK exports of a number of components related to cattle to three countries, Netherlands, Japan, and Saudi Arabia. I just wanted to show you that Saudi Arabia did import some material during the relevant period in the 1980s. This is much more clearly shown in the following graphic.

This is total imports from the UK, based on UK customs and excise data. Saudi Arabia:

· Mammalian flours, meals, and pellets. I must stress that it is often suggested that this is meat-and-bone meal. It is not simply meat-and-bone meal. It is a whole range of animal foods, which includes meat-and-bone meal.

· Carcass meat, indeed.

· Live bovines, quite a large number.

Of course, as I say, this has not been validated, but what it does suggest is that Saudi Arabia was exposed to potential BSE infectivity through imports from the UK.

Dubai, carcass meats and live bovines. Egypt, mainly carcass meat and live bovines. Bahrain, carcass meat and live bovines. Japan, very little, some live bovines. Oman, which, as David Asher said, had two cases

of imported BSE -- that is, the cattle were exposed to infection in the UK and developed clinical symptoms after export -- in this population of live bovines, which had been exported over the same period. I think it's reasonable to assume that if Oman had two cases of BSE in the imported cattle, it is possible that some of these other imported cattle may have contained infectivity.

I also put Yugoslavia up here.

Just to go back, I want to stress the scale on these slides. This is naught to 80,000, and this is naught to 800 numbers, single figures.

Just for comparison are the figures in other parts of Europe. The scale here is 1,700 times 10,000. This is number times 10,000. The scale is completely different from the exports I have shown you on the previous slide. France, a huge amount of exports from the UK, including carcass meat and live bovines. Germany, interestingly, very little, and Germany has yet to identify a case of variant CJD.

The Netherlands, quite a large number of live cattle. But it's one of the other caveats that was explained to me when this data was first shown to me. One of the big issues here is the age of the cattle when they were exported. We know from the pathogenesis study of BSE that infectivity is not present, probably, in significant

amounts for about 28 months. It is said that many of the cattle that were exported to the Netherlands were exported at a very young age for slaughter for veal consumption, and therefore, though they were UK-sourced, it's unlikely that they pose a significant risk.

Italy, very low numbers indeed.

This again is a slide from Moira Ricketts that David Asher has shown, just to stress that these export figures that I have shown are not complete. MBM -- meal, pellets, et cetera -- were exported extensively. David Asher has shown you the other figures for live bovines and carcass beef.

So it is clear that there was an exported risk. What we have not got, of course, for Saudi Arabia or for other countries are exports from other countries that subsequently developed BSE in Europe. But the level of export is likely to be very much lower than those from the UK, and therefore have posed a much lower risk, notably because the BSE incidence was so low in those countries compared to the UK.

That's the data that I wanted to present to you. I thought I would just finish on a note about the future. One of the issues that would transform the issue of transfusion transmission of variant CJD and the prevalence of infection in the UK population, et cetera, would be the

availability of a blood test. There have been developments in that region in the last few months. We have a publication from John Collinge and colleagues, “Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay,” which I won’t discuss in detail. But I think, although this is a very important development, it’s still not in a situation where it can be used in practice.

There is an interesting commentary in association with this article in *The Lancet* from Luisa Gregori, from the FDA: However, the bar for tests suitable for screening large numbers of blood and tissue donors is much higher than that for diagnostics and, as indicated by the authors, much more work is needed to develop the assay into a practical blood screening test.

But this is a development that shows promise, and also a test with apparently even more sensitivity, although not in variant CJD as yet -- I don’t think that has yet been tested -- of quaking-induced conversion, from the Rocky Mountain Laboratory.

So I think there is hope that in future years we may be in a position where a blood test may become available. But that’s in the future.

I would like to finish by thanking all the people who work at the Surveillance Unit, all my colleagues, all our collaborators in the UK and internationally, patients

and their families, without whom we could do none of this work, and the funding from the Department of Health, the Scottish government, European Union, et cetera.

Thank you very much.

DR. HOGAN: Thank you very much, Dr. Will. As always, a huge amount of information.

Are there any questions for Dr. Will before we move forward? Dr. Monroe?

DR. MONROE: A quick question on the blood recipients who are still alive. Is the genotype known for some or all of those?

DR. WILL: Some genotyping work has been done, but it is not yet available. I think that’s the best way of putting it.

MS. HAMILTON: Have there been any studies done to determine why most of the patients that have been diagnosed are in the younger age group?

DR. WILL: It is an extremely important and difficult question. There are two main possibilities. One is that the dietary exposure was age-dependent -- that is, that younger people were more likely to eat foodstuffs that contained infectivity. We believe, for example, that he most likely source of infectivity, although it is not proven, is a product called mechanically recovered meat, where bones from cattle were squeezed in a press and

extracted material, which may have contained, potentially, dorsal root ganglia, spinal cord, et cetera, was used as a filler in foods, particularly in cheaper foodstuffs. One analysis suggests that younger people were more exposed to that type of foodstuff than older people.

The other issue is whether there may be an age-related susceptibility factor in relation to human exposure to BSE. Most mathematical models, to fit the observed epidemic of variant CJD and the age distribution, require a combination of age-related susceptibility, which decreases over the age of 15, and an exposure factor.

I have to stress that this is speculative, but I think that is the likeliest explanation, a combination of factors meaning that younger people are more likely to develop variant CJD.

DR. HOGAN: One more quick question. Dr. Parisi.

DR. PARISI: You probably mentioned this. In the hemophiliacs that were born after 1989, have there been any cases of variant CJD?

DR. WILL: There have been no clinical cases of variant CJD in any plasma recipient in the UK. The only evidence of infection is in one case which underwent detailed examination of tissues after death, and that individual had no evidence of variant CJD, but was found in one sample out of a number to have the abnormal form of PrP

in the spleen.

DR. HOGAN: Thank you, Dr. Will.

I would like to move ahead now with some more examination of the Canada situation.

Dr. Coulthart, we are pleased to have you here today.

He will describe the recent variant CJD case and vCJD-related blood donor policies in Canada.

Agenda Item: Description of Recent vCJD Case and vCJD-Related Blood Donor Policies in Canada

DR. COULTHART: Thank you very much, and thank you once again for the kind invitation to come and speak to the committee today.

I would like to begin with a small caveat, and that is that the version of the presentation that was distributed about a week ago has now been updated significantly, so you may notice some differences in the last third of the talk -- nothing terribly substantive.

This is a relatively simple talk, in three parts. It basically addresses the Canadian perspective. The first portion is an introduction to the way we do surveillance for CJD in Canada and the results that we have obtained over the last approximately 13 years of continuous prospective surveillance. The second part is the case report, as advertised. The third part is an outline of the

way that the recent finding of a second variant case in Canada was interpreted and led to policy decisions, composed of a qualitative risk profile for the individual and then how we arrived at a decision on blood safety measures in the form of deferral.

It’s an indication of the complex nature of this field that CJD surveillance in Canada has received a federal funding mandate on five separate occasions, in association initially with concerns over blood safety in the late 1990s, and then later, in the 2000s, in relation to the finding of BSE in Canada. Prion diseases in Canada are both nationally notifiable, which is not a legally compelling category and provincially reportable, which is. So this helps to support the regulatory framework for the surveillance of CJD.

A comprehensive case registry as per the model that was developed in the UK and Europe in the early 1990s is the basic model. The objectives, of course, as always, are to define the features and causes of all cases of human prion disease in the country. It runs on the basis of providing support for clinicians, pathologists, hospitals, and families, largely on the provision of laboratory services, in addition to expert consultation and education. Most importantly from the standpoint of discussing today’s case, it includes a standardized interview with a family

member or other representative of the patient in which detailed background information is collected routinely.

From this combination of clinical, laboratory, and background data, we compile a database that describes that epidemiology of human prion diseases in Canada and prepares us, hopefully, for analysis and response in high-profile instances like this one.

This is a chart of the number of full case investigations, which are termed “referrals,” and confirmed cases, in the sense of definite and probable cases of all forms of human prion disease in Canada between 1998 and the last year for which reasonably complete data are available, which is 2010. You can see that although there is some fluctuation in the number of full case investigations that have taken place per year over this period, with some perhaps enhanced sensitivity that occurred around 2005, the numbers of definite and probable cases of all forms of human prion disease in Canada over that period have been reasonably steady. All of the major etiologic subtypes of prion disease have been found -- of course, primarily sporadic, which constitutes over 90 percent of the total in Canada, 7 percent genetic, and less than 1 percent acquired forms, including iatrogenic and variant.

In order to achieve these numbers, we open somewhere on the order of 250 to 300 patient files per

year, including full and partial referrals. It includes inquiries by physicians and other health professionals as to the possibility of CJD.

This is a map of the findings of the surveillance system over that same period, including also some retrospective cases, so the total numbers are larger. The main message from this slide is that it appears to be a truly national functioning system, despite the large size of Canada and the fact that we don’t have people that we deploy to investigate individual cases in person. The numbers in red are the total numbers of all human prion disease cases in those particular provinces or territories, and the numbers in blue are the ratios of the percentages of cases in that particular jurisdiction to the expected percentage based on the population of that jurisdiction. Apart from some deviations that may be explained partly by differing demography in different regions of the country, from a ratio of 1, all the numbers are reasonably close to unity. So it appears to be a fairly evenly applied surveillance methodology, even in a large country like Canada.

This is a comparison of our data for sporadic CJD with that obtained by other countries belonging to the European surveillance network. The Canadian data here, highlighted with a red circle, are in the general range of

what is found for other countries in that surveillance network, with some obvious standouts, of course, which have been noted previously. Switzerland experience in the early 2000s an elevated incidence of apparently sporadic CJD. Our data are not that different from those of the Netherlands and the UK. The methodology that Canada uses is apparently reasonably consistent with international standards as well.

The main conclusions from these data can be listed fairly quickly:

· Prospective CJD surveillance has been conducted continuously over the period of primary concern for Canada vis-à-vis variant CJD, and that is 1998 to the present.

· All etiologic subtypes of prion disease have been observed, in roughly expected proportions.

· The mortality rate has been relatively steady across time and space.

· The findings have been consistent with those of other expert CJD surveillance systems internationally.

· The system has detected six cases of acquired human prion disease, two zoonotic in origin and four iatrogenic, associated with dura mater transplantation.

· Importantly, as context for the talk today, Canada's CJD surveillance methods and data are technically sufficient, in our opinion, to address the question of

whether Canada has experienced or has not experienced domestically acquired variant CJD. You will see from the rest of the talk that the answer to that is that we do not believe it has been experienced in Canada.

On to the case report. We became aware in February of 2011 of a 24-year-old male patient with an approximately 1-year history of neurological problems. It began with a psychiatric prodrome in January of 2010 and progressed to a frank movement disorder in July of 2010, which led his father to take him to a physician for examination. Subsequently, in September 2010, he experienced rapid cognitive decline. By January 2011, when he was seen by a neurologist in the clinic, he was expressing aphasia, ataxia, profound cognitive deficits, involuntary movements, and painful dysesthesias.

Negative or inconclusive were examination for a family history of similar problems and also various routine laboratory investigations for non-prion conditions.

Tackling the question of supporting investigations for prion disease, the clinicians performed an electroencephalogram in November of 2010. It only showed generalized slowing, which was considered to be a nonspecific finding.

An MRI was conducted in November of 2010 as well. The findings illustrated a number of features. This is

fascinating to me, as a non-neurologist, in terms of the way that such patterns can vary. The signal that is sought in diagnosis of variant CJD has to do with the thalamus, in particular the pulvinar nucleus and the dorsal medial nucleus. If you just look at that area, you see this bilaterally symmetrical pattern of hyperintensity, which in isolation would be configured as the so-called hockey stick sign. It’s a little bit off the canonical pattern, from what I understand, in that the hyperintensity in the thalamus is usually expected in variant CJD to be greater than that in two other reference regions in particular, the head of the caudate nucleus and the putamen. In this particular case, you can see that those intensities are at least as high in this particular image as they are in the thalamus. Also cortical ribboning is seen, which is not a necessary feature of the MRI picture in variant CJD, as far as I understand. Of course, an expert in the area would probably tell you that the picture is much more complex than that. But this is what was found in that individual, and the neurologist did decide that this enabled the patient’s case to be ranked as probable variant CJD.

The next investigation that was requested, in January 2011, was a 14-3-3 examination of the CSF. This is the blot that we did in our laboratory in Winnipeg. We have standards on every blot, which consists of a serial

dilution of a recombinant 14-3-3 protein, beginning with the highest and progressing to the lowest intensities. This is a dilution that we include as our cutoff. We don't look at the presence or absence of a visible band on the film as the indicator of whether the patient is positive or negative for 14-3-3, but we take it as above or below the intensity of this reference band.

The variant CJD patient is indicated in two replicate loadings in these two lanes. You can see that by that criterion, although there was a faintly visible band on the blot, the patient was reported as negative for this marker protein. That is consistent with what is found more generally in variant CJD patients. The 14-3-3 assay is considered to have about 50 percent specificity for this condition. This happened to be a patient with a final diagnosis of stroke whose CSF sample was loaded on the same analysis for reference.

In Canada, just to show you that our standards are approximately the same or comparable to those of other countries that carry out this assay, the sensitivity for sporadic CJD of this assay is close to 90 percent, which is in the range of what you look for. So it's not a matter of insensitivity of the assay.

The next investigation that was done, in February of 2011, was sequencing of the prion protein gene. No

pathogenic mutations were found. Thus, genetic prion disease could be excluded by this means, because this is the only genetic locus in the human genome that has been associated with heritable prion disease to date. The genotype was consistent with other variant CJD cases to date, homozygous for methionine at codon 129 and heterozygous for glutamate and lysine at codon 219.

This was interesting. This particular polymorphism is more common in certain regions of the world than in others, particularly in southern and eastern Asia. The 219 lysine allele is more common than it is in, say, Western European populations. It has never been reported to be associated, to my knowledge, with sporadic CJD. It appears to have a protective effect against that particular prion disease.

With all of the evidence listed here, including the negative 14-3-3 and the negative EEG, this information essentially led us to the point -- combined with the patient’s young age -- of being able to nearly exclude sporadic CJD. That was diagnostically useful as well.

For those who need to see sequence data, that’s what it looks like.

Finally, a biopsy was undertaken, at the discretion of the caring physicians. Palatine tonsil tissue was taken in February 2011, on the basis of the

preexisting findings. The first investigation was by immunohistochemistry for the presence of the disease-associated prion protein. It was positive for this protein, although, as Dr. Jansen, our reference pathologist, would tell you, this was a bit of a tricky situation, because the tissue is not always received in optimal condition. He was fortunate to be able to find positive immunostaining after optimizing the concentration of the antibody for this disease-associated PrP, partly associated with visible antigen-presenting cells in the tonsillar follicle.

Finally, we undertook a biochemical examination by Western blot, and we found that the tissue was also positive for the disease-associated prion protein by this criterion. You can see the different lanes here. These are two replicate loadings of the tonsil tissue, having been treated with proteinase K to reduce the prion protein moieties to these three main components. The tissue was positive for type 2 mobility of the PrP^{res} , taking this variant CJD brain sample as a mobility standard. But it also illustrated what’s often seen in lymphoreticular tissues of variant CJD patients, and that is a preponderance of the highest-molecular-weight isoform of this protein.

John Collinge’s group at Imperial College in

London has termed this “type 4t,” for “tonsil,” to reflect the particular pattern of intensity that’s seen in lymphoreticular tissue.

I realize that this slide is somewhat redundant with following information, so I’m going to skip to the background information and not dwell on this.

Moving on to interpretation and the way that policy decisions were made, this is the way we looked at the factors that we needed to consider to assess the individual’s risk profile in terms of possible routes of exposure, including beef consumption, blood transfusion, which are both known risk factors for acquisition of variant CJD, and surgery, which is a theoretical risk factor, but not to be excluded; residence history, of course, in a broad sense, including travel. We looked at country, duration of residence, as well as dates, all as indices of exposure risk and also the possible ability to estimate incubation period from dates. Of course, the countries under consideration where the individual had resided needed to be characterized in terms of their approach to detailing the surveillance and epidemiology of BSE and CJD in their own populations, what the history of importation of bovine products was in that country, and what control and safety measures they had in place, including feed bans and specified risk material removal for

human food.

We also, of course, had to consider the possibility that some data were not available. We tried to assemble that on a coarsely graded relative risk scale, from high through moderate through low to near zero, and including unknown.

For this individual, we considered that the foodborne exposure route was by far the most highly probable, since he consumed beef regularly. Brain was included as part of a traditional diet in his family. There was no history of transfusion or surgery.

Detailed historical data were available through the family interview that we conducted, including residence history, dietary history, and medical history. Medical history from formal medical charts was not available, except for the time he spent in Canada.

Beginning at the low end of risk, we established that the risk that residence in Canada presented to this individual was near zero. He had spent a total of 1 week in 2008 in Canada and had arrived in Canada in early 2010, where he resided until his death about a week ago. His clinical onset, most crucially, predated his arrival in 2010. For all intents and purposes, in combination with the fact that Canada has surveillance systems for BSE and CJD, low BSE case numbers, and no known non-imported cases

of variant CJD, as well as regulatory measures -- all of these factors together led us to conclude that the risk of this individual having acquired his disease in Canada was near zero.

The same basic considerations applied to the US, although he spent approximately 2 years there between 2007 and 2009, because of the very low incidence of BSE in the US and also the control and safety measures that are very similar to Canada’s.

Moving on to the somewhat higher-risk countries, we considered the UK risk to be low. He spent 2 weeks in late 1995 in the UK and then another 4 weeks in 2009. Everyone in this room knows that the surveillance systems for BSE and CJD in the UK are excellent. The UK has experienced the highest number of reported BSE cases and indigenous variant CJD cases, but the measures that were particularly put in place in 1996 led us to assign a risk of low to UK residence.

In France, we considered the risk to be near zero because the patient had spent 1 week there in 2002, but no beef was consumed during the visit.

Finally, the patient spent considerable time in various countries in the Middle East, including Bangladesh, United Arab Emirates, and Saudi Arabia. We considered the risk in Bangladesh and UAE to be unknown because of,

basically, the lack of data. Even though he had spent many years, cumulatively, in those two countries combined, we could not assign any risk profile to those countries.

In Saudi Arabia, in contrast, we considered the risk moderate. This basically repeats general considerations that have already been presented this morning. The patient in particular spent a total of 11 or 12 years, cumulatively -- because he spent considerable time elsewhere during that period -- between 1986 and 1999 in Saudi Arabia. This would imply an incubation period of somewhere between 11 and 23 years, with the most probable range being greater than 19 years, if you take 1991 as the time when Saudi Arabia had banned imports of UK and European beef. There are no systematic data publicly available from Saudi Arabia, but we took into account the fact that two other variant CJD cases had been reported in Saudi residents as a proxy for the availability of surveillance data. That added to our rating of the risk in Saudi Arabia as moderate.

With those observations in mind, we took as our guiding principles, first and foremost, the precautionary approach that was stipulated by the report of the Krever Commission of Inquiry on blood safety in Canada in 1997. These are all familiar to everyone in the room, but they tend to become implicit:

· Safety has to transcend other considerations.

· Complete understanding of the consequences of hazard is not required before action takes place.

· Probability of occurrence, but also severity of consequences and potential future risks must also be considered.

· Costs, risks, and benefits also have to be balanced.

With respect to this particular case, the data strongly suggest an undocumented source of human exposure to BSE in Saudi Arabia, with the three cases with similar risk profiles, as you will see further with Dr. Schonberger's presentation. Domestic exposure is the most probable explanation for all of these cases -- that is, in Saudi Arabia. There is an unknown potential for ongoing exposure in the region.

Importantly, the Canadian variant CJD patient would not have been deferred from blood donation on existing criteria in Canada. So that represented in our minds a safety gap. There was also an argument for consistency of blood donor deferral policy. If you compare some other countries in Europe where deferral does apply and Canada, some of them have equal or comparable numbers of confirmed variant CJD cases, and other countries, like Germany, Switzerland, and Austria, with no confirmed

variant CJD cases, are also deferred in the criteria. So consistency was a factor in our minds.

In March of 2011, Health Canada enacted a change in donor deferral policy to include individuals who had spent 6 months or more in Saudi Arabia between 1980 and 1996. This was the first mandatory change in geographic deferral criteria in Canada since 2001. It was judged to have an acceptable impact on the donor base that would lead to rapid recovery of lost donors.

In summary, 13 years of surveillance data strongly indicate that Canada has not experienced domestically acquired variant CJD to date. Diagnoses of all three Saudi Arabian variant CJD patients are supported by clinical, paraclinical, and laboratory evidence. Risk profiles are similar for all three cases, with the most prominent risk factor being residence in Saudi Arabia. Evidence points towards and undocumented source of human exposure to BSE in Saudi Arabia. This was a safety gap, in our view, that required mitigation. For Canada, the precautionary principle and supporting criteria led to a decision very quickly to expand the scope of blood donor deferral.

Just finishing with some acknowledgments, Drs. Nicolas Phielipp, Tony Lang, and David Morgenthau at the University of Toronto were the attending clinicians in this

case. Dr. Gerard Jansen is our reference pathologist. Dr. Peter Ganz, whom this committee knows well, is the person who pushed the regulatory decision forward through Health Canada. Jennifer Kruse did excellent work with the family.

These are the people in the surveillance system, whose names I won't go through in detail, except to point out that Dr. Zheng Wang made outstanding contributions in providing supporting information.

I would like to finish by acknowledging some other people who contributed very strongly to our ability to come to grips quickly with this important case and to make decisions that hopefully will be useful in Canada and further afield.

Thank you.

DR. HOGAN: Thank you, Dr. Coulthart.

Are there any questions for Dr. Coulthart?

DR. HORNICEK: I was curious. How did you pick 6 months? Why not something -- how do you come up with that number?

DR. COULTHART: This tied back to some decisions that Héma-Québec had come to in late 2007. They had actually decided, without a directive from the federal level, to implement a 6-month donor deferral for Québec. One of the factors to consider there was consistency.

These numbers, of course, are highly empirical.

There is no known reason why 6 months would be a safe interval of residence in a particular country. But it's balanced against loss of donors, and Héma-Québec had found that the loss of donors since their action in 2007 was very acceptable. In the range of 1 in 10,000 donors were deferred on this criterion.

DR. HOGAN: Thank you. Dr. Kuzma?

DR. KUZMA: Along those same lines, you said consistency was one of the values that you used. But your policy on other Western European countries is over 5 years, whereas the prevalence seems more in Saudi Arabia. It didn't seem that consistent.

DR. COULTHART: I think that the answer to this -- I'm not a regulatory person per se -- has to do with how stringent you can make a donor deferral policy without counterbalancing negative effects on the donor base. So 6 months was somewhat intuitively judged -- although it was consistent with previous decisions on the UK and France in Canada -- to be an acceptable period. From Dr. Asher's slide earlier, Héma-Québec actually has a 1-month deferral interval for the UK, because it was considered acceptable to have the corresponding negative impact on the donor base to be even more stringent. So 6 months was considered to be a kind of general, middle-of-the-road acceptable criterion, from that balance

perspective.

DR. APPLEBY: Along the same lines, for the other Western European countries, the cutoff is 1980 to the present. But you had the cutoff for the Saudi Arabian donations to be 1996. I know Dr. Will showed that there hadn't been any positive cases of BSE in Saudi Arabia, but they also hadn't been excluded as BSE-free as well. What was your thinking on the cutoff date?

DR. COULTHART: Again I have to defer to my regulatory specialist colleagues for details of the background thinking. But my understanding of their thinking is that this corresponded to the period of maximum risk for Saudi Arabia as well, and it could, in fact, in principle, be extended up to the present. But it's difficult to think about exactly what constellation of factors would lead you to an alternate cutoff date compared to 1996. I think that Dr. Will and others previously made the important point that importation of UK beef may be the dominant factor in a country's risk. All of those things sort of factored into the decision.

DR. DETWILER: You said for your domestic cases of vCJD you hadn't had them for 13 years. But your risk in Canada and even for North America is actually coming in the future, really. Most of the BSE cases have been born in the 2000-to-2004 range, so you tack on incubation, probably

the concentration of the domestic BSE cases. Have you done any assessments on the potential for a domestic vCJD case and what that risk may be?

DR. COULTHART: Yes. I think I was careful to use the word “yet” when I said that Canada has not detected any domestic cases of variant CJD. Certainly it cannot be absolutely ruled out. The projections are difficult to make on such small and uncertain numbers. Some unpublished risk assessments have been performed by people at the McLaughlin Institute at the University of Ottawa. They have come up with some tentative numbers for the number of BSE cattle that might have entered the food chain, for example.

It’s very difficult to actually project with any realism what the numbers of domestically acquired cases of variant CJD in North America might be.

DR. HOGAN: I have one quick question. This individual was in Europe for 7 weeks, 2 weeks in the UK. Where were those other 5 weeks spent?

DR. COULTHART: One was in France and the other four were in the UK in 2009, I believe.

DR. HOGAN: Thank you.

Let’s break now, please. We’ll be back at 11:00.

(Brief recess)

DR. HOGAN: A couple of housekeeping issues.

(Administrative announcements)

Starting the second half here, we are very fortunate to have the preeminent neuroepidemiologist in the United States -- I hope I'm not offending anyone else -- in my mind anyway, Dr. Larry Schonberger, who is going to talk to us about the two vCJD cases that are attributed to exposure to the BSE agent in Saudi Arabia.

Agenda Item: Description of Two vCJD Cases Attributed to Exposure to the BSE Agent in Saudi Arabia

DR. SCHONBERGER: Good morning, everybody. I'm Dr. Lawrence Schonberger. I'm a medical epidemiologist and chief of the Prion and Public Health Office, Division of High-Consequence Pathogens and Pathology at CDC. One of my major roles has been, at CDC, to establish and coordinate public health surveillance for human prion diseases in the United States.

Recently, Dr. David Asher, here at the FDA, asked me to briefly summarize for your blood safety policy deliberations today information that our office had gathered on the two U.S. diagnosed cases of variant CJD in persons who were born and raised in Saudi Arabia.

Key characteristics of these two variant CJD patients are described in this slide. The first column lists the characteristics and the second and third columns describe these characteristics for each of the two US-

diagnosed case patients, respectively. As indicated on the slide, the first patient had been born in Saudi Arabia in 1970 and the second patient born there in 1983. Whereas the first case patient was a citizen of Saudi Arabia, the second was a citizen of Egypt. Both case patients were well educated and certified professionals.

The onset of the variant CJD illness of the first US-diagnosed case patient occurred in Saudi Arabia in 2003 and the onset of the second US-diagnosed case patient occurred in the United States in 2006. Since, by convention, the World Health Organization reports variant CJD case patients by the country in which they became ill, I will often refer in this talk to the first case patient as the Saudi patient and the second case patient as the US patient. Their ages at onset were 32.5 years and 22.8 years, respectively.

The early symptoms of these two variant CJD patients are listed in this next slide. Note that both patients had early psychiatric symptoms. The Saudi patient was described as initially having increased irritability, becoming withdrawn, agitated, and being paranoid. The US patient was also described as withdrawn. He had increased anxiety, for which he was seen and diagnosed by a psychiatrist, and became emotionally labile, with frequent crying. Both patients were also reported to have sensory

symptoms. The Saudi patient responded to his sensory symptoms by mutilating his skin and causing a cellulitis. For the US resident, his sensory symptoms included numbness and heat sensations in the shoulders, legs, and thigh. Both patients were described as having insomnia and developing an unsteady gait. The Saudi resident also developed slurring of his speech.

The subsequent development of dementia in the two variant CJD patients and their duration of illness are described in this next slide. Within 10 months of the onset of the Saudi patient's variant CJD illness, he was described as having, quote, global cognitive impairment, with decreased verbal output, and he was making incomprehensible sounds. His illness duration was reported to be 6.9 years, about six times the reported median duration of variant CJD in the United Kingdom and the longest duration of a variant CJD illness to date. During most of his illness, however, as indicated on the slide, the Saudi patient was reported to have been in an akinetic, mute state.

The US patient's variant CJD illness progressed more rapidly. Within 6 months of onset, he was described as having severe dementia and being nonambulatory. Among the abnormal findings on his neurological examination were increased deep tendon reflexes and ankle and jaw clonus,

indicative of the damage present in the upper motor neurons in his brain. The duration of his illness was 8.5 months. He died in 2006, the same year in which he became ill.

A summary of the most important diagnostic test results on the two variant CJD patients is described in this next slide. The spontaneous brain electrical activity patterns observed on electroencephalograms, or EEGs, of both patients consisted of nonspecific slow-wave activity. The EEGs did not show the triphasic periodic complexes characteristic of the classic form of CJD.

On the magnetic resonance imaging, or MRI, studies, both patients had a positive pulvinar sign. That is, the images showed symmetrical hyperintensity of the pulvinar, or posterior thalamic nuclei.

In 2003, neuroradiologist Donald Collie and coauthors had reported, based on the UK CJD Surveillance Unit’s experience -- and we heard some of that from Dr. Will today -- that in the appropriate clinical context the pulvinar sign on MRI was a reliable and highly accurate diagnostic sign for variant CJD. They suggested that the histological substrate of the pulvinar sign was most likely astrocytosis, which is thought to be an irreversible process reflecting a response to tissue damage within the central nervous system.

As has been reported in all the definite variant

CJD cases that have been reported to date, and as reconfirmed by Dr. Will this morning, the prion protein gene, PRNP, of both the Saudi and the US patients was genotype 129 MM, a known strong risk factor for variant CJD. In other words, both patients had inherited a prion protein gene from each of their parents that coded for the methionine, M rather than valine, V, at the polymorphic codon 129 of this gene. In addition, the genetic studies showed that neither patient had a mutation on their prion protein gene, indicating that neither of their illnesses was a familial or genetic prion disease.

The US patient had undergone a tonsillectomy at age 4 years, but adenoid tissue remained available for biopsy in 2006. As indicated on the slide, lymphoid follicles of this tissue stained positive for the abnormal disease-associated prion protein, often referred to as PrP^{sc}, or PrP scrapie. The pattern of the staining was reported by neuropathologist Stephen Dearmond of the University of California San Francisco to be, quote, identical, unquote, to those described in the medical literature for variant CJD. Although tonsils and adenoid tissues of variant CJD patients have been reported as commonly PrP scrapie-positive, such tissues in classic CJD have not been found to stain positive for PrP scrapie.

Finally, a brain biopsy was performed on both

patients. The brain biopsy specimen on the Saudi patient led to the diagnosis of variant CJD being made in the United States. In early 2004, the patient's physicians in Saudi Arabia had sought diagnostic help by shipping their patient's brain biopsy specimen to Texas, from where it went to the Mayo Clinic in Minnesota, and from there, to the CDC-funded National Prion Disease Pathology Surveillance Center in Ohio. The director of the Pathology Surveillance Center, neuropathologist Pierluigi Gambetti, observed, as indicated on this slide, that the Saudi patient's brain tissue was immunopositive for PrP scrapie and had florid plaques.

The brain biopsy tissue of the subsequent US patient also tested immunopositive for PrP scrapie. In addition, the US patient's brain tissue was reported to have, quote, pericellular encrustations of stellate-shaped cells with PrP scrapie.

These neuropathologic findings in both patients, including the pattern of the PrP scrapie staining, were reported as being characteristic specifically of variant CJD.

Even though neither patient had a full brain autopsy, nor were there any molecular typing results available by Western blot, as was seen in the Canadian case, to confirm the presence of the glycoform profile of

variant CJD termed type 2B, the evidence for the two diagnoses of variant CJD is compelling. Clinically and for surveillance purposes, each of the two cases can reasonably be classified as brain tissue-confirmed, or definite variant CJD.

The next slide summarizes the key epidemiological evidence for the most likely country where patient 1, the Saudi patient, was infected. This slide shows the countries of residence of the Saudi patient by calendar years, age, and time intervals before the onset of variant CJD. In reviewing these data, it is useful to recall that the two most likely routes of infection reported for the variant CJD cases in Europe to date have been consumption of cattle products contaminated with the agent of bovine spongiform encephalopathy or, as Dr. Will explained, in a few cases receipt of variant CJD-contaminated blood or clotting factors. Of these two generally well-accepted routes of infection, consumption of BSE-contaminated cattle products is the only one that applies to our Saudi and US patients under review because neither of them had a history of ever receiving blood or clotting factors. In addition, neither of them was a vegetarian. They both had a history of regularly consuming beef products. Both patients, for example, since 1980 had a documented history of eating readymade burgers once a week and fresh minced beef once a

month, and both patients regularly ate beef sausage, either once a week or once a month.

Insofar as one might wish to consider the extremely low possibility that exposure to variant CJD-contaminated surgical equipment might have been the source of infection in our two patients, let me mention that both patients were only operated on in Saudi Arabia. Both patients had tonsillectomies and the Saudi patient also had nasal surgery.

As illustrated in the present slide, the Saudi patient resided in Saudi Arabia between 1970 and late 1997, or, as illustrated in the second column, for just over the first 27 years of his life. Given that the Saudi patient's onset of illness was in 2003, were he to have become infected while growing up in Saudi Arabia, the interval or incubation period between his infection and onset would have been between 5.25 and 32.5 years. Both the aforementioned ages of the Saudi patient and the range of possible incubation periods indicated on the slide incorporate, as we have heard earlier, previously published best estimates for the highest-risk ages of infection and the mean incubation period of foodborne variant CJD in persons homozygous for methionine at codon 129 of the prion protein gene. As a reminder, for example, Dr. Ermias Belay and I have published in the journal *Emerging Infectious*

Diseases that 13 years was the median of the most likely incubation periods for nine such foodborne cases of variant CJD with limited periods of likely exposure. I think we heard from Dr. Will today that as time has gone on, that might now increase to 14 years or 15 years.

In addition, Dr. Valeron and colleagues in *Science* published the concept -- and this reflects one of the questions that we had earlier -- about the risk of foodborne variant CJD in persons homozygous for methionine at codon 129 being highest in persons under age 16 and then declining with age thereafter. These researchers provided no clear explanation for this relationship between age and risk of infection, but indicated that this concept was supported by the young age distribution of variant CJD cases over time in the United Kingdom and the fact that the disease only rare occurred in older subjects.

The present slide also shows that the Saudi patient was in the United States for just over a year between late 1997 and late 1998, when he was about 27 to 28 years of age. The last column shows that had he been infected in the United States, his incubation period would have been between 4.2 and 5.25 years.

Two points of interest about the Saudi patient’s stay in the United States include, first, that he did not donate blood here, although he had donated once in Saudi

Arabia, in 1991. But that was more than 11 years before his onset of variant CJD. Secondly, during his US stay, he was hospitalized for several days with a main diagnosis of aseptic meningitis that was confirmed by the collection and examination of his cerebrospinal fluid, in which there were increased numbers of white blood cells.

After returning from the United States to Saudi Arabia in late 1998, as seen on the slide, the Saudi patient did not reside in any other country before his onset of variant CJD.

Finally, note the footnote indicating that the patient had a history of visiting the United Kingdom for 4 days in late 1997 and France for 1 and/or 2 weeks in 1995 and/or 1996. Were he infected in France, then his maximum incubation period would have been 8.1 years.

As an epidemiologist, my interpretation of these data is that although infection outside Saudi Arabia cannot be totally ruled out, the most likely country in which the Saudi patient was infected was Saudi Arabia. Reinforcing this interpretation is the subsequent occurrence of other cases of variant CJD linked to Saudi Arabia.

The next slide shows the same type of epidemiological data that we just reviewed, but for the US variant CJD patient. As illustrated on this slide, the US patient lived in Saudi Arabia between 1983 and 1999, during

the first 16 years of his life. As indicated in the third column, were the US patient to have been infected during this period while growing up in Saudi Arabia, his incubation period would be between 7 and 23 years -- again, a period that incorporates published estimates of the average period for foodborne variant CJD in persons homozygous for methionine at codon 129 of the prion protein gene. This slide also shows that the US patient resided in Egypt between 1999 and late 2005, when he was between 16 and 22.5 years old. Had he become infected in Egypt during this time, his maximum incubation period would have been 7 years.

The third country shown on the slide is the United States, where he became a permanent resident in late 2005 at the age of 22.5, less than a year before his onset of variant CJD. However, as indicated in the footnote, this patient had multiple visits to the United States for about 1.5 months in 1989, and since 2001, during vacations each year, for up to about 3 months at a time. He had no history of staying in Europe.

Similar to my interpretation of the data on the Saudi patient, my epidemiological interpretation of these data is that the US patient, too, was most likely infected in Saudi Arabia.

Finally, I would like to acknowledge the many

people and organizations listed on this slide that made possible my obtaining and providing for you today the data for these two variant CJD patients.

Thank you.

DR. HOGAN: Thank you very much, Dr. Schonberger.

Questions?

(No response)

No questions. Thanks very much for your time.

We'll move along. The next speaker is going to be Dr. Luisa Gregori. She is going to talk to us about blood and blood components relative to US vCJD donor evaluation of geographic BSE exposure.

Agenda Item: US vCJD Donor Evaluation for Geographic BSE Exposure - Blood and Blood Components

DR. GREGORI: Good morning.

The next two presentations will be on current FDA donor policies for CJD and vCJD. I will go first. I'm from the Office of Blood. I will review the deferral policies for blood and blood components. My colleague Dr. Greenwald will review the policies for her office, the Office of Cellular Tissue and Gene Therapies.

In the overview of the rationale for blood donor deferrals, I will focus on vCJD, which is the topic of today's discussion, but I would also like to bring up some of the issues about FDA policies that cover both TSEs --

actually, all TSEs, all CJDs. I will also have a brief history of FDA policies and try to explain how we arrived at the policies that we have, and then current guidance, some of which has already been described by Dr. Asher, but I will go into more detail.

Transmissible spongiform encephalopathies are diseases that are transmitted by blood transfusion -- at least some of them, we know. They are very rare diseases, but they are of serious concern because they are always fatal, there is no cure or therapy, and there is no test to identify asymptomatic CJD or vCJD blood donors, although efforts have been going on worldwide to develop tests. There is also no infectivity removal technology that can be used for all cellular components. There are so-called prion filters that focus on red blood cells. Those are under development or are under evaluation in Europe, but we don’t have them in the United States. There are also limited clearance studies with TSE agents for plasma products for which FDA allowed claims, but these are on a case-by-case basis.

With this long list of what we don’t have, the only thing we have at this point is donor deferral.

What do we know about infectivity in CJD? Actually, we know that infectivity has been demonstrated not just in vCJD, but also in other animal TSEs. For a

long time we have known about the sheep infected with scrapie and BSE. In those studies done by Fiona Houston(?) in the UK, they showed that infectivity is present in sheep infected with scrapie or BSE early on in the incubation period and this infectivity is transmissible by blood transfusion. Similar studies have also been done in deer infected with chronic wasting disease.

In addition to the vCJD transmitted cases that we heard about already, there are other TSE infectivities. The question remains, is CJD also transmissible by blood transfusion? We don’t have any transmission that we know of at this point, but the question, I think, remains. In fact, there have been studies -- actually, before I get to this, I just want to show a direct comparison of the transmission rates between vCJD and CJD.

You have seen this slide before from Dr. Asher. What this shows is the vCJD from 33 patients that have been followed up in the TMER studies. These are individuals that received the blood from individuals that developed vCJD and the recipients survived 5 years or longer post-transfusion. Of these 33 cases, 4 have developed disease, 29 have no disease, and 18 are still alive. So it’s clear that there is a very high rate of transmissibility for vCJD.

In the case of CJD, we have a study done a few

years ago by the American Red Cross in collaboration with CDC, where they did a similar investigation. They followed 144 individuals that received blood from donors that later on developed CJD. These individuals, all 144, survived 5 years post-transfusion, and none of them at this point have developed CJD.

So it’s clear that there is a difference. The interpretation here is that CJD might have less infectivity in blood or has a longer incubation period or, for some reasons, is less transmissible than vCJD.

The studies -- this is not the first time it was done. Actually, there has been a previous look-back study. All the studies converge to the same conclusion, that there is no evidence for transmission of CJD by blood transfusion. However, the studies have some limitations and caveats, mostly the fact that there is a small number of patients, that there is a high rate of lost-to-follow-up -- and this is understandable, since the follow-up has to go on for many, many years because CJD has a very long incubation period -- the medical records sometimes have limited information and are not always useful, and -- very important -- none of the patients received an autopsy to rule out preclinical CJD infection.

I would like now to describe a new study. This was just recently published in *Transfusion*. This is a

study from an Italian group. They looked at the history of blood transfusion in more than 500 CJD patients. What they found was a possible association of a history of blood transfusion with CJD onset, but only in those cases in which the time between the transfusion and the onset was 10 years or longer. What they found basically was that a history of transfusion gives four times more likelihood of developing CJD after 10 years or longer. This study is the first study that ever showed a possible association for CJD related to blood or blood transfusion.

However, even these studies have their own caveats. Mostly, this type of study is prone to biases, and also to select the control cases is very difficult. These are very well noted by the authors in their publication.

We also know at this point, because it has been reported at meetings, that there is a UK study similar to the Italian study that concluded no evidence of association between blood transfusion and CJD. This study is in press. We will have to wait and see what the differences are.

Nevertheless, I thought this was important to show, because it’s the first study until now that shows an association of CJD with blood transfusion.

In conclusion, FDA policies consider all CJDs -- vCJD and CJD -- to be a threat to the blood supply, even

though we are aware that for CJD at this point there is only a theoretical risk of transfusion transmission, whereas for vCJD the risk has been demonstrated.

I would like now to move to a brief history of FDA policies. In the next three slides I will present highlights of the history and try to also indicate and point out those events and breakthroughs that shaped and sometimes informed our policies.

FDA has a very long history in CJD and vCJD policies. It goes back almost 30 years. In 1983 FDA recommended withdrawal of CJD-implicated blood components. This recommendation was somewhat based on previous, very early studies suggesting infectivity in buffy coat experimentally infected with CJD and GSS agents. In 1987 FDA recommended deferring donors treated with human cadaveric pituitary growth hormone and later other donors at increased TSE risk. These policies still are current.

In 1991 and 1996, FDA recommended withdrawal of plasma derivatives that were manufactured from pools that contained donations from individuals with CJD or with risk of CJD. This recommendation was then rescinded in 1998 because it became clear that such a recommendation could have the potential for creating a shortage of plasma proteins.

1996 was the year when the first cases of vCJD

were reported in the UK and France. Three years later, FDA had the first recommendation for residence in the UK. A few years later this recommendation was enhanced, including other European countries. This is what we have until now, with some adjustments, with some modifications.

I would like to also point out that this recommendation was in the year 2002. This was before the first reported case of transfusion-transmitted vCJD. Our recommendation was based on our knowledge at the time of infectivity in the rodent models and also the first imported case of transfusion transmission of BSE in sheep that I mentioned earlier.

There were then other modifications to the guidance, until the final guidance of 2010. This is what is the most current guidance, what you see here. This is the guidance for industry. It was released in 2010. You have there the Web link where you can find the guidance.

In the guidance recommendations, those are recommendations for donor deferral and product management. That’s product retrieval, quarantine, and disposition. The recommendations are based on risk in the donor and in the product, also take into account the effect that the donor deferral and product withdrawal might have on the supply. The recommendations are for indefinite deferral for individuals at increased risk for CJD or vCJD. In the

guidance it’s indicated that CJD includes all familial CJD-like diseases, such as GSS and FFI.

Of course, the policies also must keep a balance between the benefit of risk reduction compared with the potential adverse effects of a decreased availability of the blood supply. This is always in mind.

These are the current policies for vCJD. We have indefinite deferral for individuals that resided in the UK for 3 months or longer between 1980 and 1996, resided in France for 5 years or longer from 1980 to the present, and for both countries we also defer individuals that have a history of blood transfusion during these periods. We have also an indefinite deferral for the other European countries excluding UK and France -- those are the European countries listed here -- for 5 years or longer residence in those countries between 1980 and the present. However, these individuals are eligible to donate source plasma.

The US military also has a deferral policy. This is distinct between north of the Alps and south of the Alps. They both have 6 months, but north of the Alps it’s only until 1990 and south of the Alps it extends to 1996. This difference was recommended from DOD data that we obtained a long time ago on use of UK-derived meat in the military bases.

For CJD -- also indefinite donor deferral for CJD

risks. These risks are:

· Diagnosis of any form of CJD, including vCJD and all familial TSE, such as GSS and FFI.

· Deferral for donors who have one or more blood relatives diagnosed with CJD. In this case, a donor is eligible for reentry if it can be concluded that the CJD was iatrogenic. That means that the blood relative had non-familial CJD or if the donor is excluded to have a mutation associated with familial CJD.

· Recipients of dura mater or human pituitary growth hormones are deferred.

· Finally, users of UK bovine-derived insulin since 1980.

In conclusion, donor deferral is the only current action available to protect the US blood supply from transfusion-transmitted CJD and related diseases, including vCJD. Current US policies would not have deferred the US or Canadian Saudi cases.

I would also like to acknowledge all the people that helped in this presentation and all the people who worked at putting together this meeting.

DR. HOGAN: Thank you, Dr. Gregori.

Does anyone have any questions for Dr. Gregori relative to the blood and blood components question? Dr. Hollinger?

DR. HOLLINGER: Why is it 1980 to the present? Why the present instead of 1990 or 1996 for military and for other people?

DR. GREGORI: Why are the European countries from 1980 to the present? Is that what you are asking?

DR. HOLLINGER: Yes.

DR. GREGORI: Because we know that there is an indigenous BSE risk in these European countries. Therefore, we didn’t feel comfortable to stop the deferral to 1996, because we think they also have indigenous BSE, so there is an indigenous risk for vCJD.

DR. HOGAN: Any other questions?

DR. EPSTEIN: Just to elaborate on that point, which is correctly stated, it’s also in the absence of clear data validating control programs in many of those countries. We know that there is indigenous BSE. The question is whether the food chain is adequately controlled. We have been unable to establish that for many countries. Conversely, it was well established for UK.

DR. DETWILER: Has there been consideration -- that was my point to Dr. Coulthart, too. In North America, we have some practices. The control measures are not as in-depth as the European Union, especially the original 15. Have you looked even entirely? Given that Canada continues to have cases after most of the cases -- I think maybe all

of the cases, or at least most of the countries in Europe.

DR. GREGORI: Do you mean are we looking to Canada for potential risk as a blood donor? Is that your question?

DR. DETWILER: I am just looking for consistency of this whole thing that began with bringing it to the present, and if you are looking at the food safety control measures and the animal health control measures, reconciling them to North America as well.

DR. GREGORI: I think what we are discussing here is the donor deferrals. The donor deferrals are based on the indigenous risk that we can identify in individual countries. We have not made any decision at this point for Canada. We have not decided anything.

As far as the European countries, I think the explanation as to why we continue the deferral until the present for some countries and not others has been explained already.

I don’t know if I have addressed your question, though.

DR. HOGAN: Dr. Asher, did you have a comment?

DR. ASHER: Yes, a couple of things. In the first place, Canadian and US risks were probably identical up through May of 2003, when the first indigenous BSE cow was recognized in Canada and then later that year, when an

imported Canadian cow was recognized in the US. That risk was attributed to essentially open borders for free trade in live animals, beef products, and meat-and-bone meal. The Department of Agriculture, with whom we generally try to harmonize policies -- although we clearly have not for the United Kingdom after 1996, which is still considered a risk by the Department of Agriculture and not by us, but in general, we try to harmonize our policies with them -- they continue to restrict imports from essentially all countries of Western Europe. They consider Canada -- and Silvia Kreindel may want to comment on this -- to pose a minimal risk of BSE in any imported products. They would be in a better position than we are to comment on the reasoning behind that decision.

For Europe, there are a couple of considerations. In the first place, they are continuing to see new cases of BSE, small numbers each year, including countries that thought that they were free of it. But more concerning is the potential for cross-border importation of products, because the borders in the European Union are essentially open. We had, two meetings ago, in 2009, a talk from Marshall Plantotti(?), who explained that binding legislation went into effect in the European Union in 2001, but we were not reassured that implementation of that legislation was uniform across the European Union. We

think in countries like France, where there was prominent notoriety given to the enhanced enforcement in 2001, and in Scandinavia, where there have been so few cases, that probably enforcement is very good. But we are not reassured particularly about the new 12, where we really have no idea what the level of compliance is, and the European Union, at least in 2009, did not provide us with information about the uniformity of compliance across the European Union.

We also considered -- and I presented a summary of this in October of last year -- looking at the world animal health organization, the OIE, for some guidance about risk. But we were quite concerned that they were lumping together in the controlled-risk category countries that seemed to have quite disparate levels of risk, which was a concern to us. Furthermore, the whole system that the OIE has is currently under challenge, and it has not been accepted formally by the USDA as a predictor of true risk, presumably for the same reason that we are concerned about it. So we have not felt that we could rely on OIE classification any more than we felt we could rely on the previous classification that was offered by the so-called geographic BSE risk system offered by the European Scientific Steering Committee.

So again we are stuck with a policy that, while

it may seem somewhat arbitrary, has to take into account all the uncertainties that exist. It seemed prudent that as long as the European Union has essentially open borders and active trade in products, some of it official, some of it in the trunks of people's cars, across borders -- we felt very concerned about trying to stratify risk within the European Union, even though we recognize that some of those countries must have a very low risk indeed, perhaps approaching that in the United States.

I don't know if that over-answered the question, but that's our thinking.

DR. HOGAN: Dr. Kreindel, did you have a comment?

DR. KREINDEL: I just wanted to add a rationale, to explain what our policies currently are. We are in the process of analyzing our policies with the OIE, then to follow international standards for the importation of bovine. Although that really mitigates the risk of BSE human exposure, it will not be related to what will be allowed into this country. Basically, the OIE revognized a particular risk, based on risk assessment that was done and different mitigations in place and the presence of surveillance, et cetera. We will allow the importation based on that risk classification, but human exposure could certainly occur any time before that. It's not really related to the importation and would be mitigated.

DR. HOGAN: Thank you.

Did you have a comment, Ms. Baker?

MS. BAKER: A question. Under the two slides that talked about the FDA policy for indefinite blood donor deferral, is only one of them sufficient? I'm looking particularly at the slide that was subheaded "The increased risk," in particular, more than or equal to one blood relatives diagnosed with CJD.

DR. GREGORI: So your question is whether one relative is sufficient?

MS. BAKER: Is only one of these sufficient?

DR. GREGORI: One relative is sufficient, even if it's a relative -- if you know that you have blood relatives with CJD, it's such a rare disease that it means potentially it's familial CJD.

MS. BAKER: My question specifically is, is any one of those five --

DR. EPSTEIN: Any one of those five criteria, if met, would result in donor deferral.

DR. HOGAN: We would like to press ahead if we can, please. Dr. Greenwald will talk to us about the human cell, tissue, and products side of things.

Agenda Item: US vCJD Donor Evaluation for

Geographic BSE Exposure - HCT/Ps

DR. GREENWALD: I have a little bit of a delicate dance to do for you today. I would like to orient the committee to cellular tissue and gene therapies and how they fit into today's discussion, without trying to go back over information that has already been provided by my colleagues, and so I'm going to be referring a lot to their presentations.

I'm going to give you just enough regulatory background to explain what the products are that I will be discussing today and why we are discussing them, but then skip on through to provide information about what our donor screening criteria are for cell and tissue donors in the United States and provide some comparisons with blood donor screening and just sort of tie things together.

To start off, I always give presentations to advisory committees explaining what HCT/Ps are, or human cells, tissues, and cellular and tissue-based products. People come and go from the committees. It's a little bit more intuitive what blood and blood products are, and most of the time these discussions tend to focus around those. We have a regulatory definition that they are articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

As you can imagine, these encompass a wide variety of products, which I have here on this slide. We have products that come from deceased, as well as living donors. You will see that some of the things that we get from our deceased donors include dura mater and ocular tissues, which are at increased risk for transmitting prion diseases from the brain. From living donors we also have some hematopoietic stem/progenitor cells from peripheral blood that are considered HCT/Ps.

It’s also important to remember what are not HCT/Ps. This is also part of our regulatory definition. We are not talking about vascularized organs for transplantation. We also exclude blood and blood products from that definition.

This is just an overview of our regulatory framework for cells and tissues. With this, I really want to point out that cell and tissue donors are required to have a donor eligibility determination. During that donor eligibility determination, donors are both screened by asking questions and we ask for people to have blood tests, if tests are available, in order to look for risks of relevant communicable diseases. Just like everything, the regulations are aimed at trying to prevent transmission of communicable diseases. Mostly, the point I want to make this with slide is that the way our regulations are set up,

we only require screening and testing for agents that we have designated as a relevant communicable disease agent or disease, or RCDADs for short, because everything in my office seems to be a mouthful.

On these two slides, this one and the next one, I have summarized the current relevant communicable disease agents or diseases. This is just to show you that TSEs -- that includes CJD and variant CJD -- are considered relevant communicable disease agents or diseases for cell and tissue donors, HCT/Ps. As has already been described, we don't have available donor screening tests, so the donors are not tested; they are simply screened by asking questions.

I'm going to now jump right into explaining what our variant CJD donor screening recommendations are for HCT/P donors. You have seen the recommendations to screen for CJD, as well as variant CJD from blood donors. I just focused on the vCJD screening criteria in my presentation.

Donors are ineligible if they meet any one of the following criteria:

· If they are diagnosed with any form of CJD, including variant CJD.

· If they spent more than three months cumulatively in the UK from the beginning of 1980 through 1996.

Then we have the military criteria:

· If they resided on military bases in Northern Europe from 1980 through 1990 or elsewhere in Europe for six months or more form 1980 through 1996. In other words, it's the same as what you have heard described for blood donors.

· If they spent five years or more cumulatively in Europe from 1980 to the present. Cumulative time includes time spent in the UK. I have just provided a list of what countries we men when we say those words.

· Anyone who has received blood transfusions from the UK or France between 1980 and the present.

As you imagine, we don't have current screening recommendations regarding Saudi Arabia. That's the point of today's meeting.

To try to pull things together, I have listed here the major differences between HCT/P and blood donor screening criteria. In our donor screening recommendations, we do not exclude donors for exposure to ingested bovine insulin and we do not distinguish between France and the rest of Europe. That distinction is made in blood donors related to the difference between blood and plasma donor screening.

An important distinction to make about some of the reasons why we have these very minor differences,

especially with the bovine insulin -- I pointed out that we have deceased donors. The donor medical history interview for those deceased donors is performed by questioning someone other than the donor, and a lot of information is difficult to obtain reliably, particularly when we are talking about insulin use.

I also would like to thank my colleagues at Health Canada for helping me clarify what the donor screening criteria are for cell and tissue donors in Canada. This was brought up for the blood donors in Canada today. They do require that travel information be collected and require some donor screening for variant CJD risk factors for their cell and tissue donors, as well as organ donors. For those donors, there are no exclusion criteria based upon risk factors associated with residence or travel history to specific geographic regions. In other words, they obtain information, but they don’t necessarily require that cell or tissue donors be excluded based solely upon residence time in the UK or other parts of Europe.

Just to pull everything together, the geography-based screening for variant CJD risk is based upon evaluating the donor’s risk of exposure to the BSE agent. That’s why I didn’t go into a lot of detail about why we have TSEs as a relevant communicable disease agent or disease for cell and tissue donors. We have already sort

of made that decision, and a lot of the rationale is based upon the same things that Luisa has already talked about for blood donors. But today's discussion really is to be focused on whether or not we think that donors residing in Saudi Arabia during the timeframe discussed are at risk of having been exposed to the BSE agent.

Our screening criteria are consistent for all HCT/Ps with respect to variant CJD. They are not product-specific, so we do not need to get into too much detail about product-specific discussions today.

That's really what I wanted to bring to the committee's attention. We are asking you to think about cell and tissue donors later today.

I would also like to thank my colleagues in the Office of Blood. David and Luisa both presented extensive lists of acknowledgments, and I share those. I would also like to especially thank David Asher for his patience in revision after revision and trying to walk that fine line to make everything clear about the differences in our regulations.

With that, we'll get ready for lunch, but I want to see if anybody has any questions for me.

DR. HOGAN: Thank you, Melissa.

Do we have any questions about the cell and tissue products side of the question here? Dr. Detwiler?

DR. DETWILER: Maybe I missed this, but the cadaver donations, according to your chart, do they not get screened for TSEs?

DR. GREENWALD: All cell and tissue donors are screened for TSEs, because they are relevant communicable disease agents or diseases.

DR. DETWILER: I’m sorry, tested. I used the wrong word. Do they get tested?

DR. GREENWALD: No, there’s no checkmark beside the test because we don’t have donor screening tests available for TSEs.

DR. DETWILER: For cadavers?

DR. GREENWALD: We don’t have donor screening tests available. We don’t have blood tests. We have no tests that have been reviewed and licensed for use to screen donors, including deceased donors.

DR. HOGAN: You are suggesting brain biopsy.

DR. DETWILER: Yes.

DR. HOGAN: That has been suggested before, but it’s technically and financially pretty infeasible.

Dr. Asher, do you have a comment?

DR. ASHER: Regardless of whether it's technically or financially feasible, this came up more than 10 years ago for donors of dura mater allograft, when cases attributed to that exposure were being recognized in this

country. The problem is that there is no FDA-approved test, postmortem test. All the tests to date are considered research-use-only. The lawyers for what was then -- the product was then regulated in the Center for Devices and Radiological Health -- informed us that we could not require the use of a research-use-only test.

DR. PARISI: The neuropathology of these stories is sometimes remarkably focal, too, so you don’t know where you would take your biopsy from. I think that’s an issue.

The other issue is that the dura mater grafts are not being used anymore. People are using tissue from elsewhere or from other animals, which, you could argue, may also introduce a risk. Certainly the human cadaveric dura mater grafts are not being used anymore.

DR. DETWILER: I just find it interesting that in the animal world we routinely do screening tests for things that are probably less risky, and tests have been developed and are pretty easy to use, and still we are talking about this 10 years later, and we do different sections, realizing that the different TSEs manifest in different locations.

DR. ASHER: We have repeatedly encouraged the developers of the animal tests to validate them and offer them for human diagnostic use. They would presumably be acceptable for postmortem use. But to date none of the

test developers has done that.

DR. HOGAN: We will talk more about this when our test questions come up. Number 3 is a pretty open-based test. So we can come back to that question.

DR. GREENWALD: I'll also add on to both the comments that, if human dura mater is rarely used anymore, we do have additional requirements for use of human dura mater. Those donors must be evaluated actually by doing brain biopsies and review of those, as an additional safety measure for those tissues that are most at risk for transmitting any TSE.

DR. HOGAN: One question -- and I know the answer to this -- is there any way to estimate the effect on the donor pool that a deferral of Saudi Arabian people might have relative to any of the tissues or cells?

DR. GREENWALD: Thank you for asking that question, Dr. Hogan. As a matter of fact, I meant to bring that up at some point during my presentation. It's not on a slide, because the fact of the matter is that I have really little information to estimate the number of tissue donors we have per year or to characterize the tissue donor population, and therefore I really have no information to make estimates on how this proposal would affect the cell and tissue donor pool.

DR. HOGAN: Any other questions, comments from

the committee?

(No response)

We’re actually 10 minutes ahead of schedule. It’s unheard-of. Enjoy your lunch. We’ll be back at 1:15.

(Recess for lunch)

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

DR. HOGAN: Good afternoon and welcome to round two. I hope you all had a good lunch and you are ready to go again here.

We are going to now have Dr. David Lincoln speak with us about the potential effects of the additional donor deferrals that we are considering on the Armed Services Blood Program.

Thank you very much for coming today, Dr. Lincoln.

LCDR EMERY: While he is coming up to give his speech, if everybody on the committee can remember, we are not supposed to discuss the issues at hand outside the advisory committee table, like at lunch and in the hallways and things. So if we can try to keep the discussion here, so we can help everyone that we are here to help, I would appreciate that. Thank you.

Agenda Item: Potential Effects of Additional Donor Deferrals on the Armed Services Blood Program

DR. LINCOLN: Thank you. I appreciate the opportunity to come and talk to you guys about what we're doing in DOD and how this topic is affecting us.

I'm Lieutenant Colonel Dave Lincoln, from the Armed Services Blood Program Office here in Falls Church.

Let's take a look at our current deferral. Since

1972, there has been an MOU with the FDA, so we have been working with them. Our deferrals follow very closely to them, because our services are licensed through the FDA. We have three licenses, one for Army, one for Navy, and one for Air Force. These deferral policies will look very familiar to you:

· Residency or travel to the UK for three months from the period 1980 to 1996.

· For DOD-affiliated personnel, the risk is presumed to be a little bit higher. We defer those personnel who traveled in BSE countries in Europe for a cumulative period of 6 months or more from 1980 to 1996. One point I want to make clear is that we don’t distinguish between military bases north of the Alps and south of the Alps. We have found that it’s better to stay consistent, so we stick with one policy for all of Europe, which is the 6 months.

· For DOD-affiliated personnel, which could be dependents or contract personnel or direct-hire civilians, government employees working for the military, we defer them for a period of 5 years, from 1996 thereafter. I think Dr. Asher sort of hit that point and why we do that. There is a residual risk still within those countries in Europe, with the unknown amount of carcass meat that might be moving across the borders.

· Other personnel who have resided in or traveled to BSE countries in Europe we defer for 5 years, from 1980 to the present.

· Then, of course, transfusion in the UK and transfusion in France, from 1980 to the present.

· Anyone who has received bovine insulin prepared in the UK since 1980.

We have been tracking this. There is this new case. You heard previously about it. The patient is believed to have contracted CJD while residing in Saudi Arabia. There are two other cases that have been previously described. Héma-Québec has been deferring since November of 2007 -- the slide says 2008, but I believe it's November of 2007 -- so they have instituted an indefinite deferral similar to what you would see in Europe. DOD is moving along those lines and going to institute a very similar deferral. We have a targeted date to do that, late August, possibly early September.

Just looking back at the rationale, it's very similar to what you have seen and heard about today. Exposure to UK beef -- our commissaries at that time were importing a significant amount, even though the exact portion is not entirely known. But UK beef was available at DOD facilities, and it may have been available at a little bit higher proportion than was in the local economy.

In 1990 DOD started the process to discontinue the importation of UK beef. Primarily it was a political decision at the time. The UK had banned American imports because of steroid use, and so there was a decision made that we would reciprocate and stop using UK beef. So we began that process in 1990.

We have talked pretty extensively with the VETCOM. The vets do the public health in DOD like they do in a lot of other places. We tried to pin down exactly what was going on at that time in terms of the proportion of UK beef. It's a little bit difficult to pin down. We know that UK beef was available and that the personnel were exposed during the Desert Shield/Desert Storm time period.

The estimated proportion of UK beef to the total amount of beef is approximately 10 percent. But that number can probably go between 10 and 20 percent.

One thing to remember as well is that military personnel on the installations are exposed off the installations as well, because they typically do travel and explore. They are curious. They are in different countries, and they do get out on the economy and eat. There is a lot of that. It's very difficult to say how much they may have eaten. You have heard previously from the FDA about using dietary histories. It's really unreliable. A geographic history is basically all we have.

So it’s not known with certainty if the CJD case was related to food consumption in Saudi Arabia, but I think it’s probable that that’s the case. It’s also a possibility that other bases within the Persian Gulf may also have imported UK beef during that same time period.

Then, of course, there is the probability that third-party nations may have been involved, like the Netherlands, who purchased a large amount of UK beef and then moved that on to other countries. There are not a lot of records to show exactly where that went.

This and a lot of other information that you have heard today has us moving in this direction, where we are considering expanding the deferral to other countries within the Persian Gulf, in addition to Saudi Arabia. We have no immediate plans to do so, but we are looking at that right now.

Let’s take a look at some of the deployments to Saudi Arabia so we can get a feel for what levels of troop strength were there and what our population at risk would be.

We had a US military training mission to Saudi Arabia -- military advisers, that kind of thing -- between 1980 and 1990. Annually there are approximately 1,000 personnel deployed. Then came Desert Shield and Desert Storm, where we had a huge number of deployments. Some of

the numbers will fluctuate, but the best we can tell is that right around 550,000 troops were deployed. Ninety percent of those stayed in the area greater than 6 months. These were primarily Army troops. The ones that didn't stay were most likely Marine forces and Air Force, who at that time were in a 3- to 4-month deployment period.

Following Desert Storm, there was the continued patrol and enforcement of the no-fly zone, and approximately 5,000 deployed troops annually to support that operation.

Taking those into consideration, the total population at risk who were exposed during the period of 1980 to 1996 is approximately 590,000.

We looked at government civilians and contractors as well, and from the information that we have, which again is not as accurate as we would like -- one of the reasons is that contractors each work on different contracts. They are employed by their contractor. So the DOD doesn't always have full visibility on how many people it takes to do the job. We lay those out by tasks, and as the task gets done, whether they use 10 people to perform that task or five -- it's very difficult to see. But the nearest we can tell is that approximately one in three personnel were contractors. That's where we get the 200,000.

So taking the assumption that 5 percent of the

population donates blood -- and I think that number is from a blood utilization survey that AABB does -- you get approximately 39,500 donors that would possibly be excluded through such a deferral. Of those, approximately 30 percent, we have estimated, are already deferred, either by other deferrals or CJD deferral by the fact that they resided in Europe. A lot of the troops for Desert Storm/Desert Shield came from Europe. At that time we had a very high population in Europe. We were still in the tail end of the Cold War, so we still had high troop strengths in Germany. So it was very convenient for us to mobilize that force and move them over.

So we think that, of the population, we have 30 percent that are already deferred, for one reason or another.

We also have reason to believe that most of these individuals have already left the service; they have retired. They would have been past retirement age and have gone on to donate in their communities. Of course, some of them may still reside near military bases and still donate to our program or both to our program and to civilian programs.

Because of this, we think that the impact on the DOD blood supply would be quite minimal.

This last slide here -- we don’t anticipate that

we would need to go back and do retrospective look-backs to look at recipient look-backs for components that have already been transfused.

DR. HOGAN: Thank you very much.

Do we have any questions? Dr. Hollinger?

DR. HOLLINGER: Lieutenant Colonel Lincoln, have there been any cases of variant CJD occurring in any of our military anywhere?

DR. LINCOLN: To my knowledge, there has not been.

DR. HOLLINGER: There has not been since the rule was placed at 6 months or so. It may bring up the issue -- you said that greater than 90 percent in Saudi Arabia were more than 6 months. What would be the median of that? How many months have they been there?

DR. LINCOLN: Approximately 1 year.

DR. HOLLINGER: And that would be the same probably in Europe, too?

DR. LINCOLN: In Europe you see more of a stable population. You see dependents as well. In Europe at the time, you could expect that deployment to be about 3 years, your typical time period there.

DR. HOLLINGER: DO you have any thoughts about why there have been no cases at all -- assuming that there has been an estimate that there is a 35 percent risk of

getting beef as compared to the United Kingdom, why there have not been any cases in the military?

DR. LINCOLN: The only thing I can think of is that that number is an overestimate and that possibly because our population in general is a little bit smaller than what you would see -- so the overestimate and the smaller population. I think eventually we probably will see some cases, especially with the folks that resided in the UK and were eating commissary beef and also going downtown and living on the economy during that period. But I think it’s an overestimate, this 35 percent.

DR. HOLLINGER: One of the assumptions that might be made is that it takes a longer period of time either just for exposure or other things to contract vCJD in a group of people. We will be discussing, I think, whether 6 months or 5 years or something like this is more reasonable. The two or three Saudis that we have talked about, I think, have been in Saudi Arabia for a longer period of time. It’s just an issue that I think we will be talking about in discussion.

DR. BOSQUE: I was wondering, did the blood that is used by the military come from the same pool that the civilian hospitals use or is it disproportionately coming from the military itself?

DR. LINCOLN: It is primarily comes from the

military. We collect about 90 percent from the military and about 10 percent from civilians. So they are soldiers and sailors and airmen.

DR. BOSQUE: Does that alter the impact of the people who are deferred? In other words, will the military blood supply be disproportionately affected by deferring these people?

DR. LINCOLN: No, we don’t feel it will be. The primary reason is that the period of exposure occurred so long ago that the majority of those folks are not within DOD. I don’t know the exact amount, but I would say the majority -- at least over 50 percent -- of our soldiers and airmen that we collect from are going through some type of military training -- basic training, Parris Island, those kinds of things. They are really, really young folks. Of course, we do work with dependents of military as well. But we think most of them are probably donating to civilians right now.

DR. HOGAN: Can you order somebody to give blood?

DR. LINCOLN: We can highly suggest it.

DR. RENTAS: Just to answer your question a little more, about 60 to 70 percent of the blood supply in the military right now comes from basic trainees -- 17-, 18-, 19-, 20-year-old soldiers coming into the service. The impact is going to be minimal on DOD.

DR. MONROE: A question on that. The total number of donations that you collect per year is what?

DR. RENTAS: It's about 200,000.

DR. MONROE: A comment. I don't know if it's relevant. We heard earlier this morning that there is this sort of age risk factor associated with exposure. To the 35 percent equivalent exposure, they are young, but they are not 15, 16, or younger, where we think the greatest risk may be for exposure. The frequency of exposure may be the same, but if you multiply it by the age factor, it may be less.

DR. LEE: In one of your slides you note that the DOD in 1990 discontinues the purchase of UK beef. When you go to your slide where you look at the deployments, 1990 is really when you begin to hit your higher impact of numbers. I'm wondering if your assessment is even a little heavy-handed here as well. I don't know exactly when you cut off serving beef to these individuals, but you might be overestimating a little bit the actual exposure.

DR. LINCOLN: The best guess is that it was a wholesale discontinuation of UK beef when that came down. It was a political decision, almost a tit-for-tat kind of thing, where immediately they banned our imports and then we banned theirs.

We do kind of take a more stringent approach. It

helps with standardization as well. As I mentioned, we don't differentiate between north of the Alps and south of the Alps. We could gain a few donors if we opened that up, but our quality assurance folks are very comfortable with having a more standard approach.

You heard the previous presentations where the approximation of the risk in Saudi Arabia for that time is equivalent to what's in the UK or in Europe during that time. That's probably an overestimate carrying over.

But the issue is pertinent, because obviously we have to have ample blood supplies, and we don't think that we are going to have any mission failures because we are not being able to collect enough.

MS. HAMILTON: I just have a question. I don't remember hearing in this presentation or in some of the others where the contractors, like oil companies and that sort of thing, that are in that region -- where does that fit in, in taking into consideration the numbers of people?

DR. LINCOLN: In terms of those, they would not have been affiliated with DOD, so they certainly wouldn't have had access to DOD commissary stores. They would have received 100 percent of their beef on the economy, so they would have shared the same risk as the indigenous population.

MS. HAMILTON: Is that number included in any of

our -- as far as our people that are over there?

DR. LINCOLN: I think the issue summary has those numbers, in terms of non-DOD-affiliated contract guest workers. For our purposes, the DOD-affiliated contract workers were there less than 5 years, and so we are not deferring those. These numbers that I listed on this particular slide are only DOD-affiliated.

DR. HOGAN: I would just like to emphasize something I didn’t know before your slides came up. Beginning in the next two months, DOD will be implementing a deferral similar to the Canadian blood.

DR. LINCOLN: That is correct.

DR. HOGAN: If we could move ahead, then -- we could come back to questions if you have them -- I would like to have Dr. Yang talk with us about what these potential deferrals might have as an effect on the US blood supply.

Agenda Item: Potential Effects of Additional Donor Deferrals on the US Blood Supply

DR. YANG: Thank you.

The Office of Biostatistics and Epidemiology of the FDA conducted an analysis trying to estimate the potential effects of additional donor deferrals under FDA consideration on the US blood supply. I’m currently presenting this analysis to the committee.

Because of more limited information on donors and donations of cell, tissue, and cellular and tissue-based products, currently FDA cannot provide an estimate for the effect of donor ineligibility for the time spent in Saudi Arabia on the supplies of those products.

This morning FDA presented available information on the vCJD risk in Saudi Arabia, FDA's consideration and the justification for the consideration of additional donor deferral for time spent in Saudi Arabia. Here I would like to reiterate some key facts and assumptions that FDA's consideration was based on. Recently reported vCJD cases associated with residence in Saudi Arabia increased the concern that individuals who reside in Saudi Arabia during the period from 1980 to 1996 may have vCJD risk through exposure to BSE agent. The major risk likely came from the beef, feed material, and live cattle imported from the UK. Based on available information, we estimate about 10 percent of the beef in Saudi Arabia during 1980 to 1996 was imported from the UK.

For the US military bases in Saudi Arabia, there is a significant amount of beef from UK beef program prior to 1990. Based on available information for the US military bases in Europe, which participated in the same program, about 35 percent of the beef was imported from the UK.

vCJD risk associated with beef imported from other countries in Europe and the indigenous BSE in Saudi Arabia unknown at this time.

Based on limited information, FDA made two major assumptions. One is that vCJD risk in US military bases in Saudi Arabia is similar to the risk in the bases in Europe. Another assumption is that vCJD risk in Saudi Arabia, in general, is similar to the countries in Western Europe, except that the risk window for Saudi Arabia is from 1980 to 1996, which is consistent with the risk window period for exposure in the United Kingdom. However, the risk window period we consider for Western Europe is from 1980 up to current because of continuing reports of indigenous BSE and insufficient data in the effectiveness of the control measurement to prevent infectious agents getting into the human food chain.

Based on these two assumptions, FDA is currently considering to modify current recommendations on donor deferral to include additional donor deferral for time spent in Saudi Arabia, which includes indefinite deferral of US donors who spent 6 months or more in Saudi Arabia as military personnel during the years of 1980 to 1996 and also the other donors who spent 5 years or longer in Saudi Arabia during the same time period.

Four groups of US citizens are expected to be

affected by FDA's consideration. One is US military personnel deployed to Saudi Arabia between 1980 and 1996. These individuals include the large number of troops deployed to the First Gulf War in 1991. These individuals may be exposed to BSE agent through consumption of the beef from UK beef program. They could also go out dining locally, therefore also share some of the risks with local residents. The typical deployment for military personnel is 1 year. Currently most of these individuals have already retired from the Army. Therefore, if they donate, they will donate in the civilian blood program.

The second group is US contractors hired by US military in Saudi Arabia between 1980 and 1996. These individuals did not have access to military food facilities. They purchased food from the local market. Therefore, they share the same risk as the Saudi residents. The typical time spent for these individuals ranges from 6 months to 1 year.

The third group is US contractors hired by companies in Saudi Arabia or the Saudi government between 1980 and 1996 in the area of information technology, health care, education, finance, oil, and defense, et cetera. Time spent for this group of individuals has a very wide range of variation. It can range from months to more than 10 years.

The last group is the Saudi immigrants who came to the United States after 1985. We can see that the immigrants who come to the United States prior to 1985 would not be affected by FDA's consideration because they either have no exposure risk or they stayed in Saudi Arabia less than 5 years during the risk window period.

In the next few slides I am going to present the data, assumptions, and the approach FDA used to estimate the population from each of these four groups to be deferred under FDA's consideration.

The first group, US military personnel: Based on DOD's data, about 600,000 US troops were deployed to Saudi Arabia from 1980 to 1996 for 6 months or longer. DOD's data further indicate that 30 percent of these individuals will be deferred under current FDA recommendations for donor deferral for vCJD risk, especially the donor deferral for the deployment to the US military bases in Europe. Therefore, to calculate the number of military personnel to be deferred, we use the total number of military personnel who stayed in Saudi Arabia for 6 months or longer during 1980 to 1996 multiplied by the percentage that are eligible to donate. There is 70 percent. It is 100 percent minus 30 percent.

The second group, US military contractors: We also get this data from DOD. The data indicate that about

200,000 contractors were hired by the US military from 1980 to 1996 in Saudi Arabia. The information from DOD also indicates that those individuals are very unlikely to have stayed in Saudi Arabia for 5 years or longer. Therefore, FDA assumed that all of these individuals would not be deferred under FDA's consideration.

The third group, US non-military contractors: We got data from the US State Department on registered US citizens in Saudi Arabia in 1999. This data came from a program called Smart Traveler Enrollment Program, which encourages all US citizens living abroad to register with US embassy so they can be contacted in case of emergency. Therefore, this is a voluntary registration program. We used the data for the year of 1999 to represent the annual number of US non-military contractors during the whole period of 1980 to 1996. Based on limited information we find on the Internet, we further assume that the average time spent for this group of individuals is 4 years and 30 percent of them stay for 5 years or longer. To estimate the number of non-military contractors to be deferred, we first multiply the annual number of non-military contractors by the number of years from 1980 to 1996 and then divide by average time spent. This gives us an estimate for the total number of non-military contractors during the whole period from 1980 to 1996. Then we further

multiply the percentage of stay for 5 years or longer. That gives us an estimate for the number of non-military contractors to be deferred under FDA's consideration.

The last group, Saudi immigrants: We got immigrant data from US Homeland Security for the years 1989 through 2010. We assume all the immigrations come to the United States after 1985 would have stayed in Saudi Arabia for 5 years or longer during the risk window period. Therefore, we calculate the number of immigrants to be deferred using the equation of number of annual immigrants multiplied by the number of years from 1985 to 2011.

This table summarizes the results for the estimate of additional donor deferral for time spent in Saudi Arabia under current FDA consideration on the US blood supply. First, I want to point out that all the numbers we present here are only an approximation of the estimate for loss of donors and donations. We didn't provide the confidence interval to quantify the uncertainty, but it does not mean these numbers are completely accurate numbers.

We estimate that the population to be deferred from US military personnel is about 420,000, and from non-military contractors, about 46,000, and from Saudi immigrants, about 25,000. Multiplying this number by 5 percent of donation rate, we get an estimate of the loss of

blood donors that is 21,000 for US military personnel, 2,300 for non-military contractors, and 1,200 for Saudi immigrants. Adding them together, it's about 25,000. Then we further multiply 1.7. That is the average number of donations per person per year. We get an estimate for the loss of blood units. The total loss of the blood units for all the groups is about 42,000. The majority of the lost is coming from US military personnel, only a small portion coming from non-military contractors and the Saudi immigrants.

The major uncertainties associated with this analysis is that we don't have sufficient data for US non-military contractors. We don't have data for the annual number of US non-military contractors during the whole period of 1980 to 1996. The only data available is for the year 1999. But we believe that the number of non-military contractors will vary by years, especially will be affected by significant events that occurred during that time period -- for example, oil booming and the First Gulf War.

Secondly, as I mentioned previously, the data we got is from a voluntary registration program. That means that not necessarily all US citizens were registered. Also we don't have accurate statistics for the time spent of these individuals. The time spent varied by area of employment. For example, the contractor in education,

health care, information technology usually has short-term employment. The employment period will range from months to a couple of years. The contractor who worked in the area of finance, oil, and defense tends to have longer employment periods, ranging from 2 years to even longer than 10 years.

Another uncertainty is the data for immigrants. The data we used is Saudi-born immigrants. Therefore, it did not include those non-Saudi nationals who spent a period of time in Saudi Arabia before they moved to the United States. Two out of three vCJD cases reported were associated with residence in Saudi Arabia, non-Saudi nationals. However, we don’t expect this uncertainty will have a great impact on our estimates for the total loss of blood donors and donations because, as I presented previously in the results, both groups, non-military contractors and Saudi immigrants, only contribute a small portion of the donors lost and donations lost.

However, we did conduct a sensitivity analysis to try to see what is the impact of uncertainties on the data for US non-military contractors, our estimation for the total loss of donors and donations. This slide presents the scenario we tested in the sensitivity analysis. In the middle of the table, the most likely scenario is the scenario we used in the analysis I just presented. In this

scenario we assume an annual number of non-military contractors of 36,000. They have an average time spent of 4 years, and 30 percent of them stay for 5 years or longer. Then we add additional two scenarios. One represents the worst-case scenario, which assumed 45,000 annual non-military contractors. Their average time spent is 5 years, and all of them stayed for 5 years or longer. Another scenario is the best scenario. We assumed 30,000 annual number of non-military contractors. The average time spent is 2 years, and only 10 percent of them stayed for 5 years or longer.

This is the result for the sensitivity analysis. Under the most likely scenario, the result presented here is the same as I presented previously. The loss of blood units from non-military contractors under the most likely scenario is about 4,000. If we add in the loss from military personnel and also the immigrants, the total lost is about 42,000. Under the worst-case scenario, the loss of blood units from non-military contractors increased to 13,000 and the total lost increased to 51,000. Under the best-case scenario, the lost units form non-military contractors decrease to 2,200 and the total lost decreases to 40,000.

So if we compare the three numbers at the bottom of the table, we can see, under these three scenarios, the

numbers are not that far off.

In conclusion, the additional donor deferral for time spent in Saudi Arabia under FDA's consideration may result in a total loss of about 25,000 donors and 42,000 donations. Compared to currently 11 million blood donors, 80 million blood donations every year, this number of donors lost and donations lost won't have a great impact on the US blood supply. The uncertainty of the data will not have a great impact on our conclusions.

Finally, I would like to acknowledge all the members of our working group for OBE, OBRR, OCTGT.

Thank you.

DR. HOGAN: Thank you. Any questions for Dr. Yang? Dr. Bosque.

DR. BOSQUE: It is not so much a question, but your data highlighted something that is sort of bothering me. Of the three known Saudi cases of variant CJD, two were immigrants to North America. You estimate 25,000 or so US, maybe a few thousand more if you throw in Canada. That seems to be an extraordinarily high rate of vCJD in the group of Saudi immigrants. It's actually roughly 20 to 30 times the rate of variant CJD in Great Britain. I wonder if that means we're missing something or it's just a coincidence. It's a very low number, I know, two of three. But the rate is quite high.

It’s more just an observation. I don’t know that there is anything to answer there

DR. YANG: I think at this time it’s just because the number is still small. If you use this number to calculate the prevalence, probably it’s not that accurate.

DR. HOGAN: Dr. Salman.

DR. SALMAN: My question is about your sensitivity analysis. What did you consider for that assumption? It seemed to me, still, you are looking on the worst-case scenario, given all of the assumptions you went with, given the number of cases. You are very narrow in your estimates of the sensitivity analysis, the losses between 40,000 and 50,000. I still think this is the worst-case scenario.

What did you consider in the sensitivity analysis in terms of manipulating some of your assumptions? Did you manipulate some of the numbers?

DR. YANG: Basically the numbers. As I said, for the US non-military contractors, the information is very limited. Also the population is so different. They work in different areas. The time of stay in Saudi Arabia is so different. We cannot find statistics on the time spent. We just based it on the information on the website. All the scenarios -- every one of them was based on 5 years. That is the worst scenario. Also we looked at the

different information sources. They have estimates of the US contractors in Saudi Arabia, have a different number. The 45,000 I put in there is the highest number we saw. So I put that into the worst scenario.

The best scenario -- because we feel like this time spent is so large, so the best scenario probably is 2 years. Based on information, they say normally the initial contractor will cover 2 years. But a lot of time the employees -- the company will like the employee to have experience. So usually after they finish one term, they will give the longer employment. That’s why I put 2 years as the best scenario.

DR. MONROE: To follow up on the question about rates in the Saudi immigrants, one question would be the definition of Saudi immigrants that you are using in your --

DR. YANG: The data is Saudi-born immigrants -- born in the Saudi -- but we use this data as a surrogate. We name these immigrants. They are not initially born in Saudi Arabia. Actually, they move to Saudi Arabia and stay there for an extended period of time.

DR. MONROE: My question has to do with the definition of immigrants. Are they people who are applying for green cards? Are they people who are here on a student visa?

DR. YANG: They do not include student visas. They just utilize the US citizen.

DR. MONROE: So that’s going to be a much smaller number than the number of Saudi-born nationals who spend more than a vacation in the US and could potentially be in the donor pool.

DR. YANG: Yes, that’s a good point.

DR. HOGAN: Any other questions or comments? Dr. Hollinger?

DR. HOLLINGER: Dr. Yang, you used 5 percent as the donation rate. The largest population who are donors in this group are the military. Does that 5 percent hold for donors who were in the military and come back in this country to donate? I’m not sure I’m aware of that data.

DR. YANG: We don’t have the data. We do think about this. It seems like it’s reasonable to think that maybe military personnel come back. They may delay more. But we don’t have the data, so we just used present donation rate, the general 5 percent donation rate.

DR. HOGAN: I have one comment. I don’t know if there is an answer to it. Are there any geographic areas that might be affected more by this deferral -- that is, where there is concentration of Saudi nationals or immigrants or military people who spent time in Saudi, in any particular location? Could some region be affected

more than others? Perhaps because the blood supply is relatively transportable, it’s not going to be an issue.

DR. YANG: Do you mean the areas in the United States? I'm sorry, I cannot answer this question.

DR. HOGAN: I didn’t really expect you to.

DR. YANG: We can look at that later. I cannot answer this question.

DR. HOGAN: This is an important topic. We over a little bit in time. But Dr. Piccardo could perhaps give us some information about the questions. Then we can move on from there.

Agenda Item: Summary and Questions for the Committee

DR. PICCARDO: This presentation is intended to serve as a summary of previous presentations and to pose the questions to the committee.

As you have heard several times, three individuals who were born and raised in Saudi Arabia developed variant Creutzfeldt-Jakob disease, vCJD. On the next three slides I will briefly summarize what has been presented by Dr. Coulthart and Dr. Schonberger.

What I will call case number 1, which corresponds to the Canadian case, was an individual that was born in 1986, had short visits to the UK near the end of the UK dietary risk period. Age at onset was 23 years old. He

had a tonsil biopsy that was read in Canada as positive for abnormal PrP, and the status at the polymorphic residue at 129 of the PrP gene was methionine homozygous. The diagnosis was probable vCJD. There was no history of surgery or blood transfusion. Therefore, it was concluded that it was foodborne exposure to the BSE agent that was the likely reason for this patient developing vCJD.

Case number 2: An individual born in 1983. No history of travel to the UK. Short visits to the US and lived in the US since 2005. Age at onset, 22.8 years. Had a tonsil and brain biopsy that was read at UCSF and once again was diagnosed as positive for abnormal PrP. Once again the residue at the polymorphic site of the PrP was methionine. The diagnosis was definite vCJD. There was no history of blood transfusion. Once again, foodborne exposure to BSE agent was the likely cause of vCJD in this patient.

Case number 3: This individual was born in 1970, had short visits to the UK, France, and spent 1 year in the US. The age at onset was 32.5 years. He had a brain biopsy that was read initially at Mayo Clinic and was diagnosed as positive for abnormal PrP. Then it was sent to the National Pathology Prion Surveillance in the US at Case Western Reserve and once again was read as positive for abnormal PrP, the residue at codon 129, again

methionine-methionine. The diagnosis was definite vCJD. No history of blood transfusion. Once again, foodborne exposure to the BSE agent was the likely cause of vCJD in this patient.

For all three, the exposure is estimated to have happened in Saudi Arabia.

You have seen this slide already. I borrowed this slide from Dr. Asher. It's the crude rate estimate for vCJD in Saudi Arabia. According to this calculation, it's lower than that in the UK, Ireland, and France. However, it is very similar or identical to that in other Western European countries -- for example, Spain.

Based on current US policy, the three Saudi-resident vCJD patients described previously would not have been deferred as donors. FDA assumes that the major risk of human exposure to the BSE agent in Saudi Arabia was from live cattle and meat/products of UK origin from 1980 through 1996. The risk of the Saudi population is estimated to be less than that in the UK, for two reasons. One is, although all these calculations have uncertainties, only 10 percent of the beef imported into Saudi Arabia came from the UK for the period 1980 through 1996, and the per-capita beef consumption in Saudi Arabia is one-quarter of that in the UK.

The BSE exposure of UK origin in Saudi Arabia was

markedly reduced -- we estimate that it was markedly reduced after 1996, for three main reasons: One, Dr. Peter Soul, from UK-DEFRA, presented at a joint TSEAC/BPAC meeting in 2002, and he described extensive measures implemented by the end of 1996 in the UK to stop the spread and amplification of the BSE agent and to prevent the contamination of the food supply.

Secondly, the Commission of the European Communities, in March of 1996, published a document that says, quote, the UK shall not export to member states or third countries live bovine animals, meat/products of bovine origin liable to enter animal feed or human food chain.

Third, through communication with Saudi authorities, we were told that the Saudi authorities imposed restrictions on imports of bovine materials from BSE countries.

Based on crude rate estimates, we have no reason to think that the prevalence of vCJD in the population of Saudi Arabia is different from that in several Western European countries.

What about US military personnel? You have just heard an extensive presentation on this, so this is again summarizing briefly what has been said. Acknowledging uncertainties, FDA assumes that a significant amount of

beef consumed by military personnel after 1980 originated in the UK and decreased after 1989. We cannot assume with confidence that the original of beef consumed on US bases in Saudi Arabia differed significantly from that in European bases south of the Alps. We therefore conclude that the possible risk of dietary exposure to the BSE agent by US military personnel in Saudi Arabia is similar to that on European bases south of the Alps.

Donor loss: Again, you have just heard an extensive presentation by Dr. Yang. What are the at-risk groups affected under the proposed recommendation? US military personnel, US military contractors, US non-military contractors, and Saudi immigrants to the US. Calculated blood donor loss was a little bit less than 25,000. If we put that in perspective, a national survey determined that approximately 11 million persons donated blood in 2008. Therefore, the loss will be minimal.

Under current FDA recommendations, two Saudi-born and raised patients living in North America, of the five vCJD cases diagnosed in North America, would not have been deferred as donors of blood, blood products, and HCT/Ps. Three others, long-term residents of UK, would have been deferred. Under the recommendations considered by the FDA today, all five vCJD cases would have been deferred.

Here are the questions to the committee.

Question 1: Do available data support consideration by FDA to recommend deferring donors of blood and blood components, including source plasma, and to be ineligible donors of human cells, tissues, and cellular and tissue-based products who (a) spent 6 months or more cumulatively in Saudi Arabia as US military personnel from the beginning of 1980 through the end of 1996, or otherwise spent more than 5 years cumulatively in Saudi Arabia from the beginning of 1980 through the end of 1996?

This is followed by these two issues that are for comment: Please discuss the likely contribution of those recommendations to the safety of the products involved and the possible impact on supplies of blood, blood components, plasma derivatives, and HCT/Ps. Please comment on additional information that might better inform FDA's consideration of the proposed or any further safety measures.

I will leave it on question 1, which is the question that you are going to discuss.

Thank you.

DR. HOGAN: According to the agenda, we are going to have a short -- Dr. Schonberger, do you have something you would like to say before our break?

DR. SCHONBERGER: That was a very nice summary of

the cases and the risk. There is one point that has not been voiced. You are not a risk to the US blood supply unless you are here in the United States and here within, say, 4 or 5 years of your onset. What's interesting is that despite the UK having all those cases, there have only been three UK variant CJD cases that would fit that criterion of being in the United States within 5 years, say, of their onset, whereas for Saudi Arabia, all three of these cases were in the United States within 5 years before their onset. I don't know why that particular statistic is there, but it certainly struck me as unusual.

DR. HOGAN: Thank you for that comment.

We are going to take a break until 2:30. Then we'll come back and consider these questions.

(Brief recess)

Agenda Item: Open Public Hearing

DR. HOGAN: Good afternoon and welcome to the open public hearing portion. Before we begin the open public hearing, we would like to have a statement.

DR. ASHER: I just want to comment on behalf of the committee that set up the program for this meeting that this meeting was originally set up in proximity to the Blood Products Advisory Committee meeting that follows tomorrow. Had we known that there would be only one topic on this TSE Advisory Committee meeting, we probably would

not have set it up to conflict with the beginning of Ramadan. We really regret that.

Thanks.

DR. HOGAN: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include the company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

LCDR EMERY: Welcome to the open public hearing.

We have received one public written statement before this meeting. A copy has been given to the panel and a copy is available to be read in the public display binder at the table outside.

We have also received one request to speak during the open public hearing. It is actually going to be from the telephone. It's Dr. Gwen Stevens and Dr. Gwen Stephens and Dr. Ziad Memish. They are representing the Kingdom of Saudi Arabia. A statement that they have sent forward we will have displayed. They will be on the telephone momentarily.

DR. MEMISH: (via telephone) First, I would like to thank the panel for asking us to participate in this event. I would like to thank them all. Also I would like to acknowledge the 15 members who are present here in Saudi to listen to the deliberations this morning, from three government sectors, the Ministry of Health, the Ministry of Agriculture, and the Saudi MDA.

I'm Dr. Ziad Memish. I'm an infectious disease consultant and epidemiologist and also an assistant deputy minister of preventive medicine for the Ministry of Health. I'm now speaking on behalf of the three government sectors.

I would like to make a few points that will probably highlight some of the concerns we have with the three cases that were addressed this morning with vCJD.

A comprehensive ban on imports of British and BSE-risk countries of cattle, food, and bovine byproducts was made in the Kingdom of Saudi Arabia in May 1990. This is contradicting every single presentation that was made this morning by different speakers, who stated that the ban in Saudi was made in 1996. The ban was done through oral decree in the Kingdom of Saudi Arabia in 1990, and it was heavily enforced. Any different information will not be accurate information. This information is still valid. This is a much earlier ban compared to what was done in North America, which was 13 years later, and what was done in the UK, which was 10 years later.

The second point is, prior to the ban, imported cattle were distant for Saudi intensive dairy production. For assessment of local risk, total cattle in the Kingdom of Saudi Arabia is only 3 percent of the total livestock that we have. Unlike Europe and North America, most dietary red meat eaten by the local population is from goat and lamb. There’s no single case of BSE that has been documented in the Kingdom of Saudi Arabia.

I think these points are extremely important to be noted by the experts who presented this morning.

Now I would like to address the human cases there were discussed. According to the international agreement on the attribution of cases of vCJD, we will refer to the

three cases claimed to be attributed to the Kingdom of Saudi Arabia as a Saudi case, a US case, and a Canadian case. We would like to highlight our key concerns with these cases.

For the Saudi case, who was born in 1970, Patient GB, he was diagnosed in Saudi Arabia in February 2004. His record review confirmed a significant travel history throughout the 1990s, including significant long-term posts in the UK and 1 year of residency in Arizona, USA, in 1997.

The two other cases were diagnosed outside of the Kingdom of Saudi Arabia. We have officially requested the names and passport numbers of these cases through the embassies of Canada and the US in Saudi so that we can document their status while they were in Saudi and also their travel during the time they spent in Saudi Arabia.

The US case was born in 1983. The attribution of living in Egypt, USA, and all other travels was not estimated. Again, as I said, we do not have indications from our ministries here on the extent of travel when he was in Saudi.

The Canadian case was born in 1986. If you recall, the ban was made in 1990. It means that this case actually acquired the disease in 4 years, early in life. I think all the speakers assumed that this 4-year-old child consumed the infected meat that came from the UK in this 4-

year time before the ban was implemented, which to me is not very scientific. But then he lived in different places. He lived in the UAE from 13 to 17 years of age. He lived in Bangladesh from 17 to 19 years of age. He lived in the US from 19 to 22 years of age, and the UAE again from age 22 to 24.

I'm very surprised with the risk estimate that was made by the Canadian health authority that basically considered all these risks as non-significant, but they considered having lived in Saudi and consuming beef in the first 4 years of life as a significant and high-risk contribution -- never mind his extensive travel to Dhaka, to London, to France that was raised and considered not important, not significant.

In conclusion, we feel, in addition to the ambiguities and uncertainties about the disease, transmission risk, incubation period, and diagnostic, there are a lot of assumptions made on these three cases regarding risk assessment, which is not valid, in view of the questions about incubation period. The comprehensive ban in 1990, which I think is extremely important, on cattle imports from the UK would alter the risk assessment of the various scientific experts who made presentations this morning. We are requesting the kind attention of the US FDA. We are now compiling a comprehensive report to

answer all the points that were raised by the esteemed colleagues in the presentation this morning. They will be submitted officially, through the government, to the US FDA.

Thank you very much.

DR. HOGAN: Sir, we thank you very much, and we thank your group of associates for bringing this information to us today.

We have no other people registered for making any open public statements today, but if there are any in the audience who would like to make a statement, could you come forward now and identify yourself. And please keep it brief.

(No response)

No one. So we will declare the open public hearing session closed and move on to consider question number 1 as proposed by the FDA. I open the floor to discussion. They are interested as much in what we have to say as how we say it.

Agenda Item: Open Committee Discussion

DR. DETWILER: I have another question for Dr. Will, if that’s permissible. You had a slide up that said there has been no case from a UK patient with vCJD born after 1989. Is that correct? To your knowledge, for any of the vCJD cases in the world, have they all been born

prior to 1989?

DR. WILL: There are three cases in other continental European countries that were born after that date and were presumed to have developed variant CJD through exposure in their own countries after that date. I think the important issue here is that in many European countries, although not all, such as Switzerland, the measures that were introduced to try and minimize human exposure to the BSE were not properly implemented until, say, 2000, 2001.

DR. HORNICEK: I just want to comment on -- we heard a lot about blood and blood products, but for the human cells, tissue, and cellular and tissue products, it’s a little bit different. From each donor, you may get 100 different products that are produced. I think in some of these discussions adding that to the blood and blood components may not always be appropriate or consistent. I think it would be helpful to have even more data, as you produced with the blood and the blood products, with the HCT/Ps.

DR. HOGAN: Certainly. There are so many uncertainties on some of this data. It would be nice to know, if these deferrals are adopted -- sort of a look-back, in a retrospective fashion -- what that impact actually was in a more certain way.

Any other comments?

DR. LEE: One of the areas -- we talked a lot about blood today. I am concerned about the impact to source plasma, which has different assumptions attached to it. I didn't see a lot of data around that today.

DR. HOGAN: Does the FDA have anything to say relative to the source plasma question? It could be important. They are probably not prepared for it with any hard numbers. I guess we'll just take that under advisement.

That is the central issue in the question here, which is, does the available data support the consideration by FDA to recommend deferring, et cetera?

Any other comments?

DR. HORNICEK: Dr. Greenwald presented some data, but not to the point that we discussed blood and blood products, for the HCT/Ps. I don't know if she has any further comments.

DR. HOGAN: Dr. Monroe, do you have further comments about that?

DR. MONROE: I have a comment on the question. It has to do with -- it was sort of highlighted by our public comment folks -- is Saudi Arabia special? What other countries in the region were importing beef and products from the UK? Particularly for the US military,

are there other theaters of operation that were also importing beef from the UK in the same time period? It may be that because of the deployments for Desert Storm and Desert Shield, that's where the highest numbers are. But are there other countries?

As the public comment pointed out, there is the potential that there is exposure of one of the case patients in UAE. Do we know anything about exports from the UK to UAE?

DR. HOGAN: First of all, let me ask Dr. Greenwald to answer the question about source plasma. Then we'll go to Dr. Monroe's question.

DR. GREENWALD: Not about source plasma, HCT/Ps. I would like to clarify with Dr. Hornicek, please, what sort of data you are asking me about. Impact on the supply?

DR. HORNICEK: I think on the supply, also on -- it's a little bit different in terms of donor versus products that are produced. For each donor, it may be a lot of products. How does each of those products differ? And the transmissibility, too.

DR. GREENWALD: Starting off with the impact on the supply, Dr. Hogan did ask me about that at the end of my presentation. I will just say that that it has been troubling that we really lack that information as to how we

would impact the supply. That's something that the agency has been speaking about publicly over the past couple of years, like the emerging infectious disease workshop and stuff. We would like to try to find ways to better assess what our donor pool is like, to use for risk assessment in the future. So I can just acknowledge that that information is lacking.

As far as looking at, product by product, what the risk is for these agents, that really is a good question. But the agency has decided -- and we have had lots of past discussions about this at the TSE Advisory Committee -- that we would take an approach for all HCT/P donors that TSEs are a potential risk and that we would screen donors for those risks and exclude them from the donor pool.

I think the point that you make regarding the number of potential recipients from one donor highlights the reason why we take a very cautious approach when we're talking about these products.

DR. HOGAN: And relative to the question about UAE or other countries in the region that might have had some sort of importation of UK beef, that may be more relevant to question number 2, since that's not directly what we are voting on at this point. But I would be interested if there is any information from any FDA source

or military source relative to importation to other countries in the region. Jay?

DR. EPSTEIN: We'll address the available data from the UK. But there's a broader point that I want to make first, which is that our policies have basically been driven by where vCJD has been found. To whatever extent we may believe that three cases are probably linked to Saudi Arabia, we're focusing there. Future information perhaps could lead us to consider a broader deferral in that region or, in fact, other regions of the world, because we do know that large amounts of presumptively contaminated meat-and-bone meal went to many, many places in the world, and in many of those places BSE has not been reported -- it is hard to believe that it could not have happened -- and vCJD has not been reported. The problem that we face is that if we simply start having deferral policies based on distribution of meat-and-bone meal, where would we stop?

Again, I think the proposal really rests on the presumption that there was linkage to Saudi Arabia, which is the subject that we are discussing.

That said, there are some data, but I'm not sure that they will help us.

DR. HOGAN: That is a good point. I do remember the slide that David had showing the black, green, et cetera, distribution. It all seems to be pretty extensive

over that region.

We'll move on from that at this point, I think. Is there any other comment regarding question number 1, the amount of data, suitability for deferring? Dr. Hollinger?

DR. HOLLINGER: I have some difficulties with question 1. I would probably have to vote no, in terms of, do the available data support consideration. I have not heard anything -- we set this as an arbitrary number, the 6 months, previously. I think that was a reasonable thing to do at that time. But now we have a lot of time to view this situation. As I asked the question before, we haven't seen any vCJD in our military. We have not seen very much even from the UK, except for two people from the United States. Even that issue of the Saudis -- if a 5-year time period had been used, that would have picked those individuals up. I think 6 months, for me, is not reasonable on this.

DR. HOGAN: Meaning you think that's too short?

DR. HOLLINGER: I think it's too short. I would make it just 5 years cumulatively, like we have done with many of the others. I think it's very difficult to say, for a contractor, we are going to make it 5 years in Saudi Arabia and so on.

I think our colleagues from Saudi Arabia have made some points, in that we have ignored Bangladesh

because we don’t have any data from Bangladesh. We don’t know if they might have acquired their infection in Bangladesh. I think there was another issue about Egypt, although, as I looked at the data from Egypt, it looked like it was later, maybe even past 1996.

To me, there are so many issues that make it difficult for me to support a recommendation for 6 months or more cumulatively in Saudi Arabia for the US military.

DR. HOLLINGER: I will remind you that they did say that very few of the military people were there as long as 5 years. It’s also the association of how much they ate during that time period.

Jay, did you have something you wanted to say relative to that 6-month period?

DR. EPSTEIN: Yes. The way the FDA has been approaching the issue since 1999 has been to try to reduce the number of risk-weighted exposure days in donors. What we have tried to do is look at relative risk. This was mentioned by Dr. Asher. As the benchmark, we have simply taken UK, because it has been the geographic area of highest risk, for all the reasons that you already know. So the concept has been, if we assume -- and, of course, it’s a simplifying assumption -- that risk is simply proportionate to time spent times relative risk, we then convert that to how long you need to have been exposed to

have a risk equivalent to UK.

Where we went with DOD personnel in bases in Europe -- essentially, we rounded off 35 percent and called it 50 percent and doubled the time from UK exposure, 3 months, to DOD exposure, to 6 months. That was an effort to get at relative risk.

What’s really being said here is that we find it hard to distinguish the risk of soldiers exposed on bases in Saudi Arabia from the risk to soldiers exposed on bases particularly in Southern Europe, simply because there was a beef sourcing policy. That’s the sum total of it. We do know that the procurements decreased post-1989, but we can’t say exactly to what extent.

With respect to 5 years, as has been said, the concept has been proportionality, if you will, to Western Europe. This comes back to this estimate of cases per population. Once again it all rests on the assumption that these three cases are most likely associated with exposure in Saudi Arabia, and this is an issue in its own right. But assuming they are, then if we look at it as a per-population risk, not understanding all the factors that might go into that, it aligns with countries such as Spain.

Why 5 years? Again, the estimate that was made for France -- and this goes back to the earliest days of the deferral policies -- was about 1/20th the risk. So 3

months UK times 20, 60 months, 5 years. Again, the underlying assumption is a linear proportionate risk with exposure, offset by relative intensity of exposure.

But as has been pointed out earlier by Dr. Asher, the relative risk in certain parts of Europe was known to be lower. For example, our risk estimate for Switzerland was .015, 1.5 percent of UK risk. How did we get to that? We got to that because they had good numbers on BSE surveillance, and we were comparing BSE.

What we actually did for Western Europe was that we said, well, it's going to reign somewhere between some very low number, perhaps comparable to Switzerland, to some higher number, perhaps comparable to France. We chose the worst case. We simply said, we'll treat Western Europe as if it's France.

The issue then arises, if we are trying to do something comparable on the assumption of risk in Saudi Arabia, where would risk in Saudi Arabia lie? We're simply saying it's like Western Europe, and we are therefore treating it like France.

There is one subtle point here about source plasma. With respect to France, we continue to defer source plasma donors who have had 5 or more years of exposure. We do not do that for the rest of Western Europe outside UK. That was in deference to the relative risks

and benefits, recognizing that there was significant clearance of prions in manufacturing demonstrated by model systems. So we balanced, if you will, the expected donor loss versus the benefit of clearance and essentially said that the deferral policy might give us at best 1 log risk reduction, but the clearance from manufacturing is giving us, we believe, 4 logs or greater. So we traded it off. But we made exception for UK and France, just because they were the areas of highest risk.

So the inclusion of a deferral for source plasma donors under the current suggestion in question 1 is, in effect, saying Western Europe-like, but more like France. Why more like France? Because in France most of the risk was driven by importation of UK beef, whereas for the rest of Europe most of the risk was really driven by their indigenous BSE. So to whatever extent you might think it’s France-like, you would lean toward the more stringent side. If you think it’s more like the rest of Western Europe, then you would say don’t include source plasma. And that would be consistent with our policies for the rest of Western Europe outside UK and France.

I’m simply trying to make the logic clearer. I don’t think this resolves underlying questions, how you interpret the data and how you might advise the FDA, but I just wanted the logic to be transparent. Risk-weighted,

donor exposure day, that’s the underlying heartbeat.

DR. HOLLINGER: But, Jay, again you are making your assumption on modeling and so on. I’m making my assumption on actual data -- no cases. How do you pull those two things together? Over the 10 or 15 years now, we have not seen any cases either in the military or in other people who have come to this country. That’s the kind of information I would like to see.

DR. EPSTEIN: Well, I take your point. There have been many exposed soldiers, none of whom has presented with vCJD. That’s puzzling. Conversely, it was pointed out that if you look at the incidence of vCJD in immigrants from Saudi Arabia, it’s remarkably high. Maybe some of this has to do with food consumption patterns.

I can’t explain it either, Blaine.

There’s another concern, though, which underlies these policies, which is that some individuals who may never develop variant CJD might harbor latent infection which might be blood-transmissible. Again, that’s theoretical. It’s a worst-case assumption, and it has never been shown. But we do believe that there are latent infections, and we don’t know if they are blood-transmissible.

DR. APPLEBY: So the timeframe between 1980 and 1996 -- it’s assumed that that is when the highest risk of

imported BSE-contaminated beef was for the UK. The rest of Europe is 1980 to present because of some suspicion of BSE surveillance. What do we know about Saudi Arabian BSE surveillance? It's not on the OIE list for either BSE-free or presence of BSE cattle. Also they just report now that they have been cleared by the OIE, that they don't have BSE. But it's not on their website. How does that factor into it?

DR. ASHER: As far as I know, what the Saudi authorities mean is that they recognized no cases and reported them to the OIE. One presumes that they really haven't recognized any cases. The last time I checked, they don't have a categorization by the OIE. That whole system is under challenge, not by Saudi Arabia, but by Korea. That's because the OIE system runs on voluntary submissions of files to the OIE to evaluate.

I don't believe that Saudi Arabia is a significant exporter of beef products, which probably means they are not highly motivated to go through the effort of preparing a submission.

We were discussing the good news that out of, we estimate, over 4.8 million US service personnel stationed on bases in Europe over the possible risk period, there haven't been any cases. There are at least a couple of things that come to mind.

One, it’s conceivable that the quality of the beef imported from the UK was better. Bob may comment on this. There is an interesting gradation in the United Kingdom that suggests that those populations that ate more meat that was likely to have been contaminated with risk material are at higher risk for variant CJD than those who ate more expensive cuts of meat. So that’s possible.

Another interesting possibility -- and we commented on this early -- is that we haven’t age-adjusted these populations. The general population of Europe, of course, ranges from zero to old age. The military does not. You are not eligible to join the military until age 17 at the very earliest, so there are no children who were exposed, except some dependents in Europe. Certainly in Saudi Arabia there were no children who would have been exposed to the imported UK beef.

We have a problem if we try to reach conclusions about the risk for those military personnel on Saudi bases based on the failure to see cases in the US military. As Jay pointed out, of course, the incubation periods can be very long, and the period in which infectivity is present in blood is at least 3.5 years. But we don’t know how much longer. The second thing is that in order to adjust that logically, we would have to adjust the recommendations for all the bases, not just the Saudi bases, because I don’t

know a rational basis for concluding that the Saudi bases were safer than the European bases.

But I assure you that we frequently discuss the whole policy. There are a number of other issues with the policies, not appropriate to discuss today. Certainly that one will be under consideration into the future.

DR. BOSQUE: Getting back to the principles upon which the original time intervals were based, if I understand right, the risk in France was estimated at about 5 percent of the risk in Great Britain, and then that number was derived from that. But the data would say the risk is about 14 percent of the risk in Great Britain.

Similarly, as we have all said, the three cases identified in Saudi Arabia seem to be a very select population -- or associated with Saudi Arabia; I know they are not all from there originally. It makes it difficult to know really what the rate is in Saudi Arabia. The rate is estimated to be approximately the same as other countries in Europe, but there is an enormous amount of uncertainty around that number. I just want to point that out.

We are dealing with a lot of vague information here, necessarily vague. It’s just inherent in it. But sticking by these principles that were originally, I think, about 10 years ago -- it’s possible that these intervals

should be adjusted, based on the actual empirical evidence we have now.

DR. HOGAN: I think that has been a consideration and it has been a point that the FDA has been considering. The issue as put to us in this question -- I'm sure they are taking notes -- is the numbers as they are presented. But I think it's important that they are hearing from us about those very issues.

Dr. Detwiler, you had your hand up.

DR. DETWILER: I think this whole thing of basing it on the UK is bothering me, for a couple of things. I looked over the numbers in Dr. Will's presentation again. If you look at the exports of the UK, one, the live cattle -- somebody mentioned it might be import the cattle and slaughter the cattle -- they are 1984 and before. So the live cattle as it was -- that's for sure not the highest risk period. There were many countries that imported many more cattle than that. But even the meat, the bulk of the meat prior to 1984 -- there was some after, but it does seem to be just two small shipments after. We don't know -- but it was carcass beef, which you would think would not be more your high-risk tissues on that. If you look at Egypt, their importations of carcass beef are much higher, and even countries like the Netherlands in Europe, and yet you don't see that effect.

I think tying it to the UK -- I'm uncomfortable, just because either some people there were just extremely unlucky or something is wrong with that hypothesis.

DR. HOGAN: Dr. Will is not here. Dr. Barraj?

DR. BARRAJ: I might be able to answer the question. In terms of imports, you also have to look at the population basis where it's going. The Egyptian population size is obviously very different from the Saudi population in terms of base population. That could explain why the much larger number going to Egypt is not reflected in a higher number of incidences.

DR. DETWILER: Right now, if you look at all the experts around -- in fact, the OIE says you can trade carcass beef pretty much from undetermined-risk countries, regardless of amount of BSE in them. So they have pretty much ruled that that's safe meat in itself, unless at the time -- like you said, Dr. Will is not here -- was there something else going, and how did they define carcass beef?

DR. SALMAN: I have a few comments, mainly one related to why we see this in civilian and less in the military. If you think carefully here, we have two different populations. The military, whether in Europe or in the Middle East, has a high standard of the type of meat they can import and they can use. I'm not in the military, but I know from the Veterinary Corps that that's how they

do things. Even if they are importing from the UK, they are not importing what we call the specified risk materials. That's almost a big no even from the beginning, because that's not related to the diet they are expecting.

So that's one important thing here we need to consider, why we don't see a lot in the military in that way.

The other thing is the issue related to BSE and how OIE is reporting. OIE is a volunteer agency, in some way. It is not like it has police authority to request that every country has to report if they have a BSE case. So a lot of countries could have BSE cases and they will be either misdiagnosed or intentionally not reported. That, I think, is an important aspect that should be considered. That doesn't mean the country is BSE-free. That's the reason, actually, whether it's the OIE or even the European Commission, when they started about the BSE status, decided to do risk assessment in order to determine if the countries could be considered at the risk of having BSE or not. They still think that way. It's not like to say, well, this country is free from BSE.

The other important aspect -- I don't think, when you look on the occurrence of BSE, it's not related specifically to the live animals, neither to the importation of meat. It's mainly related to the meat-and-

bone meal. The importation of contaminated meat-and-bone meal is specifically from Europe, and particularly from UK. In the beginning, when the MBM, the meat-and-bone meal, was banned in UK, they did not ban it in the other countries. UK was exporting very cheap MBM to a lot of other countries, like Singapore. Singapore had only one dairy farm at that time. The importation of the MBM to Singapore is unbelievable, when you look on the Europe status, how many thousands of tons of MBM went to Singapore. Singapore is used as almost a source of the -- like as almost a bypass. Import it to Singapore and then they will send it to other countries.

A lot of countries in need of dairy products -- and the dairy products will require dairy farming, and the dairy farming will require animal source protein, such as the MBM. These countries start to import whenever they find the cheap protein. So that’s another issue that we need to consider before any type of a decision on whether the risk in one specific country is more than others.

Finally, you talk about other countries, and especially in the region. Bob Will presented that, showing that Bahrain, United Arab Emirates, and Egypt, as well as Saudi Arabia. To my knowledge, when you look on the dairy population in these countries, Saudi Arabia exceeds three of these countries in terms of the concentration of dairy

farming, which will require high concentration of ration or diet to these cows. That high concentration of ration will require source of animal protein or high-protein diet. Most of this will come mainly through the meat-and-bone meal because it was cheaper than getting soybean, for example, just to make it clear at least for some of you to understand the situation.

DR. HOGAN: Thank you. Ms. Hamilton?

MS. HAMILTON: I have a question. I'm not clear on the relationship, if there is one, of the 6 months or the 5 years to the long incubation period of vCJD.

DR. HOGAN: Does anyone have any thoughts about that? I think they are totally separate. The issue is restriction based on how much time you spent in the country. The incubation period is disease-related.

DR. PRIOLA: The 6 months to 5 years is exposure time, when you would be exposed to infectivity. From time of exposure to onset, that's incubation period. That's how they are separated.

MS. HAMILTON: My concern was not being able to know for that length of time after they come to this country.

DR. HOGAN: Again getting back to the issue of whether the two numbers should be the same or different.

Dr. Monroe?

DR. MONROE: Just in response to Dr. Epstein's clarification, the question is worded this way, but is it fair for me to consider this by rephrasing it to say, do the available data support consideration of military personnel in Saudi Arabia to be equivalent to military personnel south of the Alps and for other residents of Saudi Arabia to be equivalent to residents of Europe other than France? As he pointed out, we are looking at relative risk, and you are saying that the numbers were based on coming up with -- those risks would be relative to what we're seeing in Europe and in the military south of the Alps.

DR. EPSTEIN: Yes, I think that's the underlying heuristic. I don't think we need to reframe the questions necessarily, as long as everybody understands that that's what the proposal means.

DR. MONROE: My point is, if I was starting de novo, I might say that the data don't necessarily support that. But based on your points -- are the risks comparable? -- then I might say, yes, they are.

DR. HOGAN: I like that analogy. I think we can all assume that.

DR. KUZMA: I have a question about the Japanese case of variant CJD. I notice that the person was in the UK for 24 days or something to that effect. I'm wondering,

again from this risk comparison perspective, why the travel of the three Saudi cases to the UK -- I guess two of the three had spent some time in the UK. I'm wondering, what was the rationale for trumping the time in Saudi Arabia over the time in the UK, given that that Japanese case had such a short travel time to the UK as well?

DR. ASHER: In the analysis we attributed that case to Japan, not because we are necessarily convinced that infection was acquired in Japan, but we decided that you have to draw the line someplace and we decided to use the convention that has long been used by the UK CJD Surveillance Unit. If you start trying to attribute cases to the UK, a lot of the cases that are in other countries in Europe would have had short trips to the UK, and then the whole effort to attribute to the most likely country of exposure comes apart and the uncertainty becomes simply impossible to deal with.

There have been over 30 cases of BSE in Japan. If a country had no BSE at all and one was confident in their status, you might draw a different conclusion.

By the way, we have, ourselves, occasionally referred to the Japanese case as the closest thing we know to a point exposure by the dietary route. So we agree that there is a possibility that the person was actually exposed in the UK. But the same thing might be true for other

countries for which we don’t have that kind of information.

DR. KUZMA: I heard a lot of the assumption that they were exposed in Saudi Arabia today, whereas --

DR. ASHER: You look at the time of exposure and try to figure out, particularly in early childhood, what exposure period covers the most plausible time of infection. Judging from incubation periods with a median or 12, 13, 15 years, the longest period of exposure that is plausible puts all three cases in Saudi Arabia. But we made the point that we can’t be sure of that and it’s not impossible that they were infected in other places.

DR. KUZMA: Can I follow up with that, on a clarification? What is our donor deferral policy for -- we don’t have one for Japan. Is that correct?

DR. ASHER: No. We briefly mentioned the possibility of having -- we have no travel information for Japan. Of course, deferring for one case of variant CJD or for the 30-some cases of BSE, now that both Canada and the US have BSE, becomes less easy to estimate. The same question came up when Israel found a BSE case. We just have no travel history. The impression was that it might make a significant impact on donations in certain areas -- for instance, Honolulu and some cities on the West Coast -- if we attempted to defer for residence in Japan. I suppose we did consider it highly likely that the Japanese case was

infected during his short trip to the United Kingdom. Theoretically, there is no reason why one contaminated meal could not infect a person, just as one contaminated injection is sufficient to infect an experimental animal.

DR. HOGAN: Dr. Bosque?

DR. BOSQUE: This sort of relates to Dr. Monroe's reconceptualization of the question. It looks like the determination of risk for military personnel is really completely separate from the determination of risk for people living indigenously in Saudi Arabia. Then I'm wondering, by adding Saudi Arabia to the places where military personnel may have been stationed that potentially could be a place with infected -- does this cover all the places now that would have gotten UK-sourced beef or are there other military bases elsewhere that would be, on the basis of where they got their beef supplies, also at risk?

DR. RENTAS: The questions that we are asking here are the same questions that were asked three or four months ago when we met and we brought the transfusion medicine consultants from the Air Force, the Navy, and the Army, and everyone from the Armed Services Blood Program, including the quality people. As you heard in the presentation, we have decided to follow the same donor deferral policy that Canada has at this point.

To answer your question directly, Bahrain is one

country that we are looking at closely, because, as was shown this morning, there was a large amount of cattle imported into Bahrain. The Navy specifically has been in Bahrain for quite a long time. However, when you look at the big picture, Saudi Arabia by far is where we have the most people in the Persian Gulf area. No one comes even close to that. A big part of that is Desert Shield and Desert Storm.

When we came to the deferral policy of 6 months -- all our collection facilities are FDA-licensed. That means we have to follow FDA policy. Current FDA policy is 6 months, even for countries where you haven't had a single vCJD case out there. We have been following Saudi Arabia now for about two or three years. When the third case was associated with that country, we felt that we needed to be consistent with that policy by implementing a 6-month deferral.

The bottom line, to be honest with you, is that the impact on the DOD supply is very, very minimal, because most of these people are either retired or they are not on active duty any longer.

DR. HOGAN: I can see the bumper sticker now: Is there BSE brain in Bahrain?

I had to wake a few people up here. Dr. Priola.

DR. PRIOLA: I want to go back to the issue that

Dr. Kuzma brought up about the one case in Japan. We have no deferral policy for Japan. We have no deferral policy for Canada, which has two cases. There are three potential cases associated with Saudi Arabia. Statistically there can't be any difference between one case and three cases coming out of those countries. So what is the driving force behind wanting to institute a potential deferral for Saudi Arabia when we're not doing it for Canada, which really only has one fewer case? Or was one of those cases a Saudi Arabian? Right, one was a -- but Canada has BSE. I understand the exposure times and whatnot. But still, even then, one case versus three -- statistically, that's just not very strong. So what is the overriding piece of data that causes the FDA to consider deferral for military personnel in Saudi Arabia? I really don't see what it is.

DR. COULTHART: Just a small point of clarification. Both of Canada's cases of variant CJD were considered imported, one from the UK and the most recent one from Saudi Arabia.

DR. PRIOLA: It still leaves the issue of the one case in Japan. I understand from what Dr. Asher just said that they assign greater weight to the 2 weeks in the UK. But that does seem like a matter of opinion, in a way.

DR. ASHER: Japan is the only country that has had a vCJD case for which we have no deferral. The reason

for that was that we couldn’t estimate the effects on the donor population in important cities, but we thought that it might be considerable. As I pointed out, it’s true that you can’t assign the case to the UK based on the international criteria, but we all suspect that that’s where the case was acquired because of the time in which the patient was there and the fact that there were 12 years between the 24 days and the onset of infection, which is a relatively plausible incubation period.

DR. PRIOLA: So obviously the impact on the blood supply would be much greater if you deferred --

DR. ASHER: We thought that in Honolulu, San Francisco the impact might be considerable. The donor survey that had been done in 1998 and 1999 couldn’t be extrapolated to make any predictions at all for donors who had been to Japan.

DR. PRIOLA: So if you institute a deferral for Saudi Arabia, does that substantially decrease risk here in the United States for transfusion-transmitted variant CJD? Deferring those few people, does that affect at all the relative risk?

DR. ASHER: The total risk reduction would be small, because we don’t think there are very many blood donors who spent shorter periods of time in Saudi Arabia.

By the way, I might point out that, as Colonel

Rentas pointed out, not just for the military, but the total population of Saudi Arabia is very large compared to all the other countries of the Arabian Peninsula, except for Yemen. We think that the number of contractors and immigrants entering the United States and donating blood from Saudi Arabia is likely to be considerably larger than those from Yemen. I think, taken together, Kuwait, the Emirates, Bahrain, Qatar have fewer than 15 million residents today, whereas Saudi Arabia and Yemen together have more than 50 million total population at the last estimate.

DR. HOGAN: I'm letting this go, because some of these comments are pertinent to 2 and 3 as well. But we have spent a long time on this. Hopefully nobody is upset about that.

Are there any others?

MS. BAKER: Are there any published data on donor patterns, donor characteristics of Saudi immigrants to the US or elsewhere?

DR. HOGAN: I don't believe so. Does anybody have any specific information on Saudi blood donors? No, is the answer I'm getting from FDA.

Comments? I am assuming, then, if we move on to a vote, that we would take both parts A and B together as one vote.

DR. EPSTEIN: No. We would like you to consider each part.

DR. HOGAN: Fine, good. Is everyone comfortable? Any other comments before we go ahead and vote on question 1, part A? This is taken *in toto* -- and maybe Dr. Monroe, after I'm finished, can rephrase it; I like your reconstruction -- do available data support the consideration by FDA to recommend deferring donors of blood and blood components, including source plasma, and to determine to be ineligible donors of human cell, tissue, and products --

DR. EPSTEIN: If I can be permitted, Dr. Monroe, if we just add a phrase at the beginning: by analogy to risks in Western Europe, do available data support.

DR. HOGAN: Okay, you have permission. Then part A -- donors who spent 6 months or more cumulatively in Saudi Arabia as US military personnel from the beginning of 1980 through the end of 1996? Essentially it's voting yes or no.

(A vote was taken.)

DR. HOGAN: So the total number of "yes" is 12 --

LCDR EMERY: The total votes are 16. Sixteen voted. There are 12 yes votes, there are zero abstentions of the 16 eligible voters, and there are four that voted no.

Dr. Hogan voted yes. Dr. Rentas voted yes. Dr. Parisi voted yes. Dr. Detwiler voted no. Dr. Kreindel voted yes. Ms. Baker voted yes. Ms. Hamilton voted yes. Dr. Barraj voted yes. Dr. Salman voted yes. Dr. Priola voted yes. Dr. Kuzma voted no. Dr. Monroe voted yes. Dr. Appleby voted yes. Dr. Bosque voted yes. Dr. Hornicek voted no. Dr. Hollinger voted no.

DR. HOGAN: Thank you very much. We'll move to part B: Based on the analogy to the risks in Western Europe, do donors who otherwise spent more than 5 years cumulatively in Saudi Arabia from the beginning of 1980 through the end of 1996 deserve deferral?

Dr. Detwiler?

DR. DETWILER: That is not at least the way I read the FDA's policy for Western Europe. It's to the present, correct? That's my big problem with both of these. It's to the present, other than the UK. Even France is -- is that not correct?

DR. EPSTEIN: Yes, that is correct. Again, the distinguishing thought is that this may have ended with importation of contaminated bovine products from the UK no later than 1996. We are basically saying risk is otherwise like Western Europe, but did end.

If the committee disagrees with the deferral as proposed, the committee can propose an alternative.

DR. HOGAN: So Dr. Detwiler brings up the issue, should it just be through 1996 or should it be 1980 through the present? Is that what you are suggesting?

DR. DETWILER: Yes. The same thing with the first one. Western Europe is to the present, so it's not fully equivalent to that. Do you see what I'm saying? That was my problem with that. That's what I'm saying. We tie part of this to the UK and then the other part of it to Western Europe. That's where I have the problem with these.

DR. HOGAN: Of course, that would extend the effect of these deferrals considerably if you were to include people during that entire time period.

DR. DETWILER: Right. The first one, the reason I voted no on that is because I thought if you are going to do it equivalent to Western Europe, why do such a short period of time as 6 months? I wanted the first one to be a longer timeframe, on A.

DR. HOGAN: The current question as stated is, I think, what we have to vote on. Then they can take all of this discussion under advisement. So we will vote, then, on part B here. The answer is either yes or no. Is everyone clear on this? We can vote now, please.

(A vote was taken.)

DR. HOGAN: Does industry have any comment? The

answer was no.

LCDR EMERY: The committee has voted. There are 16 total votes. All 16 have voted. There are 15 that voted yes, there are zero abstentions, and one that has voted no.

Dr. Kuzma has voted no. The rest of the committee has voted yes.

DR. HOGAN: Thank you.

Now we can go on to the more free-range type of discussion, some of which has already been brought up. I think there are some important points that some people might want to expand on, however.

Point 2 here is, please discuss the likely contribution of these recommendations to the safety of the products involved and the possible impact on supplies of blood, blood components, plasma derivatives, and human cell and tissue products.

We don’t know what the effect on human cell and tissue products is. Hopefully we can get some retrospective information from people like the eye bank, et cetera, that are deferred when they come in and fill out their questionnaire. That’s easily obtainable material. That would help us know the actual impact.

Other comments? What does this do for the safety of the blood supply? It has already been asked. Dr.

Monroe.

DR. MONROE: I think the question was asked. Probably the answer is, little, for what we know about, which is for the donors and recipients that are methionine-methionine homozygotes. I think the one consideration is the stuff that we don't know about, which is the potential for the second wave with folks who are methionine-valine or valine-valine. There may be an impact on the safety for those people that we don't fully appreciate.

DR. PRIOLA: Just to follow up a little bit on that, Dr. Epstein mentioned earlier that the FDA believes that this disease can be latent, which is possibly connected to the genotype at 129. But I would just like to clarify, what exactly do you mean by latent? I used to be a herpes virologist, and latency has a very specific definition for me, and that is, an infection that really isn't active, even though the virus is there. Do you mean more subclinical or persistent or low-level replication?

DR. EPSTEIN: It's loose talk. We just mean that during the long incubation period, the presymptomatic incubation period, of infection, we do have evidence certainly in the animal models and some human that there is high lymphoid association and possibly a blood phase. So the question is whether there could be transmissibility from blood in an asymptomatically affected individual.

DR. PRIOLA: So infectivity is always present.

DR. EPSTEIN: Right.

DR. KUZMA: I just wanted to make a comment, because I seem to be the troublemaker here. I think this is going to improve the safety, however minuscule. The reason I voted no is that I don't think the data support this. I think what we are really after here, just being explicit about it, is precaution. That off-chance that one particular unit is contaminated -- it's really more of a fault tree than it is a play of numbers. So I had to vote no on the first question, although I'm happy that the blood supply will be probably more protected, however minuscule that probability is. It's a precautionary measure. That's my view of it anyway.

DR. HOGAN: I think even those of us that voted yes agree with you. Certainly there are a lot of uncertainties in the data. But this hopefully will have some effect on the safety of the blood supply.

DR. KUZMA: I just feel like we have to make that value explicit. The data is important. It's important that we understand the evidence. But I think the value here is really what's driving the decision.

DR. HOGAN: Other comments? Ms. Hamilton?

MS. HAMILTON: I just have to make a positive comment. Those of you who have known me for any amount of

time know I go back a long way, and when I heard three, you can imagine that it took me back to 1981. Had everybody acted then like they are acting today, we could have saved a lot of lives. So it's very important to me that we do this now and for anything else that comes up.

DR. HOGAN: Thank you. Dr. Detwiler.

DR. DETWILER: I actually think probably this whole exercise should be taken further. We have kind of been alluding to it as we go around. I know for animal health issues with BSE, where you don't have really good tests and all the trade, we have to look at this whole thing on a holistic, global view, to look at countries that have high risk factors, but may not have good surveillance systems. I would think that's appropriate here if we are going to be protective, because there might be regions of the world, if you look at that map -- you look at Asia. The amount of material that went to Asia for risk factors -- and so if their public was exposed, but they don't have good surveillance, they could be much more of a risk than some of these other countries. I would think that that's probably a prudent thing as well.

DR. LEE: I want to get back to question 2. One of the things mentioned earlier about source plasma -- frequently the commercial plasma centers are in proximity or may be in proximity to military bases. These donors

tend to be robust, reliable, conscientious donors. I do have a level of concern because there is no data describing the impact on source plasma today presented to the team. I did want to bring that forward to the committee to be aware of and to think about. That then translates to impact to plasma derivatives.

I personally right now couldn't give you an impact risk, or even a high, low, or medium. Frankly, I just don't know. But the data today really didn't get at the source plasma and the ultimate impact to that. I appreciate what Jay said about utilizing the French approach to making the decision. But the data today really didn't look at source plasma strongly enough. Again, as everyone on this committee knows, there is a lot of high-frequency donors. If you start excluding them, you are actually reducing those units, it could be, pretty precipitously.

DR. HOGAN: I agree with you, and I'm glad that that comment was made. Perhaps the issue about source plasma should be taken separately.

DR. LEE: That's exactly what I'm asking. Thank you for bringing that to a point.

DR. HOGAN: Any other comments?

(No response)

Essentially, I think you are hearing from us that

the safety of the US blood pool -- it will be safer. The military has already taken this step. They certainly will be safer, albeit maybe the retirees are no longer in the military and donating to the military pool. But there are some steps that could be taken to make it even safer. Look at other countries. Look at BSE surveillance issues, et cetera.

Are there any other questions that FDA would like relative to question number 2 that we have not discussed or beaten to death?

(No response)

Number 3 is even more open-ended. Does anybody have any objection to going on? No.

Please comment on additional information that might better inform FDA's consideration of the proposed or any further safety measures. Dr. Bosque.

DR. BOSQUE: Two points. Both have been brought up before, but just to emphasize them because I think they are appropriate to this part of the question. I think it would be a good idea to revisit those original recommendations from 1999 or whatever year it was -- we now have 15 years worth of data on variant CJD -- using, maybe, the actual numbers to reformulate those relative risks. The modeling is fine, but, really, there are so many unknowns, I think the hard numbers are much more reliable.

The second thing is, it is striking that these three Saudi-associated cases came from a very, I would think, unusual socioeconomic group. Either other cases are being missed in Saudi Arabia or there is some special risk factor in this group. I think, maybe working with the Saudi health authorities, it would be really worth looking into this more carefully.

DR. HOGAN: Good comment. Dr. Salman.

DR. SALMAN: I just want also to add, the reason I voted yes for both of them -- mainly to maintain consistency with what we applied way before related to other European countries. However, way back, I voted no for this issue about any type of deferral for anybody in Europe. But I was in the minority. Actually, I was the only one. Since we have that, we should maintain the consistency. That’s the reason I voted yes today. But I think -- it’s mainly to add to this -- we need to maybe review now the data and see how much is really this type of issue, and deferral from the blood supplies or even the plasma derivative -- how much is really contributing to reducing the risk, in general. I’m not trying to say it would not reduce the risk. But we need to think carefully, is it really worthwhile to continue with this policy or this type of strategy? If we go with that policy, we need to also maintain good records and knowing countries and

what they report.

I really don’t know about human diagnosis, and I wish Bob was here in this room. But I can tell you, there are a lot of countries where the new variant CJD could be misdiagnosed or could be even not recognized by even physicians there. By focusing on countries, either we see them here and we diagnose them or they are honest and report cases. We know from the animal side dishonesty in reporting is well, well known. We need to have a much better idea before we decide on how we will go with that.

That’s maybe what I will add for information in the future.

DR. APPLEBY: Pertinent to that, outside of North America and most European countries, there is very little human surveillance whatsoever. Surveillance is one thing, but then if you pick up a case of variant CJD and don’t report it, even outside of surveillance, then we don’t know.

DR. HOGAN: That is the key, surveillance both for vCJD and BSE. I would be interested in having USDA perhaps bring up some of their data again at some point regarding surveillance issues, not only in other countries -- now adequate those may be or may not be -- but also here in the United States. I have some concerns about that.

Any other comments?

DR. DETWILER: I have two things, and they are totally unrelated, on surveillance, but it's also -- I go around to a lot of other countries and get in the slaughterhouses, and a lot of countries that do not find BSE take no protections for public health. They don't pull out high-risk material. That's another really big risk factor for their human population, then for this exposure to result in variant cases. So I think it's not only surveillance, but even the factors in the human health protections in these countries.

DR. HOGAN: High-risk meaning spinal cord --

DR. DETWILER: Yes. There are a lot of countries around the world that, because they are BSE -- they have no BSE, then they don't feel that they have to take any of the high-risk tissues out.

Then I have another totally -- unless --

DR. HOGAN: You're up.

DR. DETWILER: I want to go on the record to say -- and this is about for the tissue donors. I was on the committee when this issue was first brought up about cadaver and testing. I understand FDA -- there's no approved test. But there are technologies that can do these tests. I'm incredulous, actually, that we don't test, do brain biopsies or some type. We have so much now

technology to do that, in order to test them, in order to make sure -- now, we're not going to pick up everything, if there is incubation or whatnot in there. But at least the positives you get. We have so much new technology. I still can't believe, in human medicine, we're not doing that.

DR. HOGAN: I presented to this committee on that very issue. For instance, there are 40,000 cornea donors per year. If you did a brain biopsy on every one of those cases -- 20,000, let's say, that donate both eyes -- how are you going to do it? We thought about going through the nose. Maybe you can get frontal lobe. Is that going to be the best place? Maybe going through the back, getting cerebellum. Is that going to be the best place. So it's a sampling issue, then it's doing the test, then it's collating the data, and doing it all in a timeframe -- these things are only good for 4 days.

That's one example. Someone else said it's not really a financial or technical issue, but it does come down to a technical issue.

DR. DETWILER: In the animal world we slaughter I don't know how many thousands per day, and in the European Union they have to have it. They slaughter it one day. In order to release the carcasses within probably less than 24 hours they have to have the test returned in order to do

that. There are probably 7 million tests done per year.

DR. HOGAN: I think there is space for an entrepreneur there.

Any other comments?

DR. HORNICEK: There are also a lot of incidental findings. For example, for most of the people who come in to see me, it's an incidental finding that really has no clinical relevance, but it can be very challenging as to how to deal with that problem. So a cautious expense, but also what are you going to do with the data that you obtain?

DR. HOGAN: Any other comments? Anything. This is pretty open-ended.

(No response)

DR. HOGAN: Is FDA satisfied, at least for today?

DR. EPSTEIN: We are very grateful to the committee for its deliberations and recommendations. Thank you.

DR. HOGAN: I also would like to thank the committee. You have been sitting here for a long time. Everybody has kept on time. I appreciate the speakers' ability to do that. I thank everyone that presented at the open public hearing, both submission *in absentia* and locally. I look forward to the next time that we see each other. I'm not sure when that will be. Everybody have a

safe trip home, and thank you so much.

LCDR EMERY: Thank you, everybody, for coming.

(Whereupon, at 3:53 p.m., the meeting was adjourned.)