They had to be sold into other scrapie-monitored flocks. That was the thing. They could not sell any of the original imports. They could sell progeny into other scrapie-certification flocks. So there were nine sold.

Of these nine animals sold, there were seven ram lambs. We did go out and contact the owners and purchase all those and destroyed all those animals, took samples. There were two ewe lambs and another ram lamb sold to another premise. Because there were ewe lambs that lambed in this flock, we asked the owner and purchased this entire flock as well, again with the transmission of scrapie.

These samples have been tested from this flock and there was no evidence of disease. But there were three actual progeny into this third flock.

[Slide.]

Other product, cheese, was sold throughout the United States. These were predominantly East Frisian milk sheep. They were manufacturing cheese, especially the larger farm, and selling throughout the United States. Then, prior to the quarantine, there were 45 carcasses that went for human consumption. I will talk more about those.

[Slide.]

This is just to show you the breakdown. They came in in 1996 but didn't start lambing until '97 because they were young when they came in. This is a breakdown of how

many lambs, when they went and the poundage. The poundage I put on here just to give you an idea of the age. So they would be six months or less.

The last two shipments that went for slaughter, we were able to bring the carcasses back after the European Union opinion and then we destroyed those, or the last two shipments.

So where did they go? Where did these go? They were sold at two local stores, like mom-and-pop outlets. They were sold off-farm. None were sold through the internet. 10 percent of the sales off the farm went to friends, acquaintances and tourists, and the family and their attorney consumed the product. They are in court with us, now, too.

[Slide. 1

What happened after the quarantine? We bought all, then, the culled, sick, picked up the deads. In these situations, in order to milk sheep, I just want to explain, you have to keep breeding them. So they produce young and then they produce the milk. So we did get a lot of offspring in the meantime from when they went under quarantine; in fact, over 300.

But what the USDA did with those is we purchased them like we were the slaughter outlet because you cannot have a quarantine--that, by the way, was applied by the

State of Vermont--unless you give an outlet. So we purchased them like a slaughter outlet and incinerated the carcasses. So we have been doing that ever since. Anything that was older, that was culled, sick or died, we sampled it and then incinerated the carcasses.

The results? On histology, we found in some of these vacuolated neurons, astrocytosis and neuronal degeneration. By regulation, in the USDA, we have to have, for TSE, scrapie diagnosis, four confirmed lesions for histology. Most of the sheep had one of the lesions, two of the lesions. One had three, but none had all four. So there was no regulatory basis that we could act upon these sheep.

There was capillary electrophoresis, again, I just want to emphasize. But this has been talked about publicly and, also, in court. There were blood-positives on some of these sheep and that was done, even though the test is under development, at the request of one of the owners who said, "Test my sheep because I think it will clear them."

Lo and behold, we did have six sheep that came back blood-positive. We took brains, then, from those sheep that were positive by the CE and tested those under our regime of testing, and four of those tested positive by the Western blot analysis. That was done by Dr. Richard Rubenstein, with whom we have a cooperative agreement, at

the Institute for Basic Research in Staten Island, New York.

The Western blot done by actually had a little hearing of its own. Would you like to see the Western blot, the committee? You have to click in the middle. I couldn't figure out how to cut and paste this on.

Why don't we go on. Then I will come back and try and get it up there for you to take a look at.

[Slide.]

So what happened? This happened in July of this past summer, the Year 2000. We approached the owners--at that time, there were the three flocks in existence, the one with the ewe lambs and these other two--to ask them to voluntarily depopulate the flock.

By the way, the entire time from when they started to be under quarantine and even prior to that, we had asked them if they wanted to sell the flocks to us and that we would pay for the flocks, just to remove the risk. They chose, at that time, not to do that. So, even up to before this, they were asked if they would depopulate those flocks.

Then, after the positive diagnosis with the Western blot, because that is, for us, a legally binding test, the owners were asked one more time to voluntarily depopulate. The small flock, the one with the progeny, did agree, so those sheep were removed, as I told you earlier.

Then, on July 14, the Secretary of Agriculture

declared an extraordinary emergency. That is what we need, in the USDA, in order to seize property. So an emergency order had to be declared for us to obtain money. Orders were then issued by the Department to seize the flocks, the two flocks.

[Slide.]

One of the things here, now, I will talk'to about is what it is we found. The tests that we have run, so the histology, the immunohistochemistry and the Western blot, they don't differentiate between different strains or variants of scrapie from BSE. So these tissues would, too, then have to go in mouse bioassay. So we don't really know what disease we are dealing with here.

It was named this atypical, because of the histology. We had Gerald Wells from the U.K. look at the histology and that is one of the ways he described it; "TSE of foreign origin." The foreign origin came into play because these sheep came in as groups and there was no exposure to U.S. animals or U.S. product.

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What happened next is really history because it really played in the media. The two owners went to court for a temporary restraining order. The judge denied the temporary restraining order, as I said. There was even a hearing on the Western blot test. He did not grant the

temporary restraining order.

However, he asked them to voluntarily comply. They did not. So then we had to go back to court and ask for a motion for an order to comply and for the judge to rule on the merits. So we filed final briefs at the end of December and we are waiting on a court decision.

By the way, they have been maintained, again under quarantine and under surveillance, with the same protocols in place, that anything that dies, anything is removed, we get and sample.

How about if I try and bring that Western blot up?

That is all I have.

[Applause.]

DR. BROWN: Thank you, Linda. We will look for the Western. One question, Linda, and that is in the history, had there ever been a prior case of scrapie on those farms, ever, before the imported sheep came?

DR. DETWILER: I should have probably talked about the history of the flocks. They came out of about ten different flocks in Belgium and the Netherlands.

DR. BROWN: No; I am more interested, actually, in the U.S.

DR. DETWILER: oh. No, no. They were brought in for different premises where we had no reports of ever having sheep there, nor were they commingled with anything

here. They were brought in as separate groups for this purpose.

DR. BROWN: So, essentially, it is virgin pasture.

DR. DETWILER: Correct; at least to the best of our knowledge.

DR. BURKE: What is the reluctance on the part of owners to voluntarily depopulate?

DR. DETWILER: They do not believe, and I am just paraphrasing so--they do not believe that there is a problem in these flocks. I will give you a history--I think that might help, too--on the situation in Europe. We did go back and try and get a lot of information. We haven't been that successful of getting information from the government. We have requested it, but they have said they have got their hands full with other things right now.

One of the things that we did find from just getting other data from sources like the veterinarian that signed the health certificates, that they were fed concentrate. So we do know that, that they were fed concentrate made in local mills that did produce both ruminant and non-ruminant feed, although we have certifications that said they didn't include ruminant meat and bonemeal in the feeds at least since certain amounts of times when the feed bans went into place.

so we have those, but there is a likelihood, in

Europe, of cross-contamination. They did come in with scrapie certification statements, that they had been monitored. But even now, since that time, we have found that some of them have not been monitored as long as they nay have seemed to have been. So there is some question, even on exposure to scrapie.

[Slide.]

This is the Western blot. I couldn't get the other block. He had that on a separate one, the fourth sample, on a different one. I'm sorry. I got one to go but I couldn't get the other one, to bring it with me.

DR. RRUSINER: Could you explain--

DR. DETWILER: I can only explain the three positives because this is Rich's stuff. These, I think, are two sheep from there that he did call no--these three, he caused positive. And then, over to the side, are some of the controls.

So these three, at least what Rich explained in court, were the three that he called positive. These two were also sheep, as I recall, from the flocks. You know what? I don't know much about Western blot. Bob Roher, he helped with the thing and the Western, so he probably could answer more, or you can talk to--

These, I believe, are controls.

Any other questions?

DR. ROOS: Two questions. First, how many other flocks were imported during this window.

DR. DETWILER: That's it.

DR. ROOS: Oh; this is it?

DR. DETWILER: This is it.

DR. ROOS: The second is how did these come to your attention? Were there sick animals or you pursued them because you know them came in?

DR. DETWILER: When things change, one of our jobs is to monitor what is changing in science and what is changing in the world. One of the things we noticed, as the science changed in '96--oh, by the way. That is a good point you bring up. At the end of '96, when the publication of Foster's paper that showed that it was not only in brain and spinal cord, when it was in spleen, then we thought, "Oh, oh; it might be--" and the paper suggests that maybe, if BSE became natural in sheep, that it could spread like scrapie and then feed bans wouldn't control it.

So we, again, shut the door at the end of '96 to all sheep and goat imports with the exception of going back to the same countries, Canada, Australia and New Zealand.

DR. BROWN: Thanks very much, Linda.

The next presentation is entitled, efforts to contain and eliminate chronic wasting disease from farmed cervids given by Dr. Creekmore of the APHIS staff, USDA.

Efforts' to Eliminate a Program to **Eliminate CWD from Farmed Elk**

DR. CREEKMORE: Thank you.

[Slide.]

I am really not going to be able to talk too much to you about products, so, in terms of products and distribution and where they have gone, what we have discussed this morning is the best information that we have right now. But I was asked to give a USDA APHIS Veterinary Services overview of our efforts to initiate the program to eliminate CWD from the farmed-elk industry.

I will probably go really quickly through these first few slides because much of this was covered already this morning and I don't want to belabor things that we have already been through. But I would like to give you a little bit more information on our surveillance efforts to date in the farmed-elk industry as well as where we are with this development of a program.

[Slide.]

Dr. Miller summarized what we know about the distribution of this disease in free-ranging deer and elk and the fact that we have an endemic area that is fairly well defined. However, what I want to move on to is how recently we have found CWD in farmed-elk herds in multiple states in the U.S. and Canada. He also depicted that but I

maybe will show it to you in a bit different way.

[Slide.]

CWD was first detected in the farmed-elk industry in the U.S. in South Dakota in 1997. Since then, the disease has been identified in thirteen farmed-elk herds in **Eive** different states. The last positive farmed-elk herd was identified in late April of this year in Colorado. At this point, nine of these elk herds--or, actually, excuse me; of last year, April of last year in Colorado.

At this point, nine of these elk herds have been depopulated or have gone to slaughter in testing..

[Slide.]

Six were from South Dakota, one in Montana, one in Colorado and one in Nebraska. That leaves four herds that are remaining, one in South Dakota, one in Colorado, one in Nebraska and one in Oklahoma. Also, as was mentioned this morning, the one herd that is left in South Dakota is slated to be depopulated.

[Slide.]

USDA's support of surveillance has included both farmed and free-ranging cervids. Dr. Miller included our efforts to support farmed-elk surveillance in his summary this morning. In terms of farmed cervids, we, USDA APHIS, have tested about 2,500 animals since the latter part of **1997**, so starting with our fiscal year '98, which would be

starting in October of '97.

As you can see, surveillance numbers have increased each year. The 339 figure represents from October through December of this year.

[Slide.]

Many of the submissions have been from the North Central states and most have been from farmed-elk operations. The numbers of submissions are somewhat reflective of states that have initiated surveillance or certification programs. So far, there has been very little surveillance in the farmed-deer industry. CWD has not been identified in deer from the farmed-deer industry yet but we really need to be doing surveillance to have assurance that it is not there.

We are trying to encourage increased surveillance in both the farmed-elk and deer industries and surveillance will be a key component of the proposed herd certification program. However, efforts have been hampered by the absence of a national program as well as the lack of indemnity.

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Key areas of USDA APHIS Veterinary Services focus and response regarding program development have been prioritized based on resolutions from the U.S. Animal Health Association or the USAHA. This association has requested action from federal and state agencies to address the CWD

issue.

In 1998, USAHA recommended a model program for surveillance control and eradication of CWD in domestic elk. This model was for use by the states as a template for their CWD programs and it was a model that was developed by the North American Elk Breeders Association. It is what Dr. Zebarth described to you this morning.

They created this model in association with the states and others including some state wildlife agencies and USDA representatives. Then, in 1999, USAHA requested that USDA and the states develop a CWD herd-certified status program for farmed-elk based on this NAEBA model.

[Slide.]

In response to the 1999 USAHA resolution, USDA APHIS has begun to develop such a program. In the past year, we have submitted a budget for a CWD program as a new line item for FY 2002, so that would be starting in October of 2001. At this point in the process, the submitted budget will be enough to establish a framework to support a CWD program for captive elk but won't be adequate to cover indemnity.

Then, in terms of program development, itself, in March of last year, we brought together a Veterinary Services CWD study group. This group took the NAEBA model and revised it. Like the original model, our VS revision

included certification with increase in status based on surveillance as the basis for the program.

However, the revision encouraged the more aggressive approach of depopulation of positive herds rather than quarantine as the primary response. This revised program developed by the VS study group was then taken to a group we called the National CWD Working Group for'input. That was in June of last year.

This group was composed of stakeholders including representatives of the farmed-cervid industry as well as the exotic wildlife industry, state agriculture and wildlife agencies, university and USDA ARS representatives. The objective of this meeting was to obtain input on the framework of the certification plan that we had adapted from the NAEBA model.

That objective was met and a revised plan was produced. We took this most current draft back to the original VS study group, back to the national working group, circulated it to federal and state veterinarians, industry associations and representatives, producers as well as to others and asked for input which we have received.

What I would like to do now is briefly summarize the framework of the proposed program.

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The APHIS proposed program is designed to address

the farmed-elk industry and it will use a herd certification program as its basis. The basic requirements for participation in the herd certification program will include fencing to enforce separation from free-ranging cervids, animal identification and herd inventory with annual verification, diagnostic surveillance of all deaths of animals over sixteen months of age.

Herd status would be based on the number of years of such surveillance with no evidence of CWD. Herd additions would be allowed from herds with the same or greater status and a positive herd diagnosis would be based on post-mortem brain testing performed by the National Veterinary Services Laboratory or NVSL-approved laboratories.

[Slide.]

If a positive herd is detected, the preferred option in the proposed program is depopulation of the herd with payment of indemnity. An alternative option is a five-year quarantine with selective depopulation of high-risk animals if they are able to be identified. In the case of a quarantine, it would be required for a herd plan to be developed. This herd plan would include inspection with removal and testing of any clinical suspects, surveillance of all deaths that occur in the herd, animal ID and inventory and additional fencing requirements.

If a herd is a traced-forward or traced-back herd, there are also requirements. For a traced-forward herd, the preferred option is removal of the trace animal with testing. If that traced-forward animal is negative, then the herd enters the certification program for further surveillance. If the animal is positive, that herd is treated as a positive herd.

Then, also, an option for a quarantine, as I described, for a positive herd is possible. Then, for a traced-back herd, a five-year quarantine with a herd plan as I described above.

The industry, at this point, has requested that, as we continue to develop the federal CWD program that we build into the program a prohibition on the sale of velvet, meat or other food products from quarantined herds.

[Slide.]

In terms of interstate movements, within this plan, we want the states to be able to have the disease Legally reportable and have ability to quarantine for the disease if it is detected. With this particular program, as proposed, the producer will have to be a participant in the herd certification program to be able to move his or her animals interstate.

In lieu of a national program, a number of states have instituted CWD programs and many others are in the

process of developing programs similar to that I just described--in other words, based on the NAEBA model or on the USDA proposed program model. Dr. Miller also covered that a bit this morning.

So, various levels of surveillance and certification of herds currently exist in some states. There is basic underlying support for the USDA CWD program from the industry and others and, for the most part, there seems to be basic agreement that a program is badly needed and that this proposed program provides a good framework to take further in the process.

[Slide.]

USDA APHIS will continue to support surveillance of farmed and free-ranging cervids. We plan to continue to support development of improved diagnostic tests and other research. We plan to continue the process of developing a mutual framework for CWD epidemiological data-collection needs on a national and international basis and, in September of this last year, we began this process by convening state, federal and Canadian epidemiologists and veterinarians working on CWD epidemiology to share information on current CWD work and information needs.

In addition, we will continue the development of the national CWD program.

[Slide.]

At the USAHA meeting this past year, in October, we presented the proposed program in a resolution requesting that USDA APHIS continue to develop and implement a federal program for the eradication of CWD in farmed-elk with the provision of indemnity was passed. In response to this 2000 USAHA resolution, the VS CWD study group will be meeting again in February of this year to create a final draft of the proposed program taking into account and incorporating input as appropriate so that the process of drafting regulations may begin.

We plan to implement this program in FY 2002 or starting October of 2001.

I would be happy to answer any questions.

[Applause.]

DR. FREAS: Since our chair is out of the room, can we hold the questions and go on to the next speaker. There is one more speaker. When our chair is back, he will lead the discussion of the questions, if you are going to stick around, Dr. Creekmore.

Our next speaker is Dr. Robert Moore speaking on regulation of ruminant materials in U.S. dietary supplements.

Regulation of Ruminant Materials in U.S. Dietary Supplements

DR. MOORE: My name is Robert Moore. I am Chief of the Dietary Supplements Branch in the Division of

compliance and Enforcement in the Center for Foods at FDA.

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I have been asked to summarize the current information that we have concerning the status and the use of animal-derived ingredients including those of bovine origin in dietary supplements.

I have several take-away points that I want to just communicate up front. First, FDA is the responsible federal agency for regulating the safety of dietary supplements and the agency has the regulatory and legal authority and tools to act against unsafe products.

Dietary supplements may lawfully contain some animal-derived tissues and such products, both of domestic and foreign origin, are known to be marketed in the United States. The information that we have from domestic and import inspectional activities indicates that most bovine-derived ingredients do not originate in areas in which BSE has been identified.

Fourth, FDA recognizes that there are emerging public-health issues that it may need to consider with respect to the use of these both bovine and other animal-derived ingredients in dietary supplements.

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I first want to talk about some of the basic legal definitions and the framework that applies to dietary

supplements since the 1994 amendments. There are many dietary supplements being marketed in the United States that contain animal-derived ingredients. With some exceptions, most of these products appear to be lawful in that they appear to contain dietary ingredients that are defined in Section 201(ff)(1) of the Food, Drug and Cosmetic Act as amended by the 1994 Dietary Supplement Health and Education Act.

DSHEA, which I will simply refer to as DSHEA, rather than saying it each time, defined the term "dietary supplement" to mean, in part, that it is a product that would contain several named ingredients; a vitamin, a mineral, an amino acid, an herb. But the definition also states that legitimate dietary ingredients include "a dietary substance for use by man to supplement the diet by increasing the total dietary intake of that substance."

[Slide.]

Finally, it also defined dietary ingredient to include a concentrate metabolite constituent extract or combination of anything previously named in that section of the statute. What the term "dietary substance" means, however, is not addressed directly in the statute or in the legislative history that accompanies it.

Therefore, the term must be defined in accordance with its common, usual meaning. We have tentatively

interpreted that term in the statute using an understanding of the ordinary meaning of the words that were included by Congress in the definition; namely, that dietary means if you go to a Webster's, or a Random House, or pick a source, dietary means "of or relating to the diet."

The term "diet" means an organism's usual food or drink. The word "substance" generically refers to; "that which has mass, occupies space and can be perceived." So, when you take that in the context of the statute, the term, from a legal point of view, a dietary substance simply means the common-sense understanding of the term.

It means substances customarily used as human food or drink. Many animal-derived tissues and substances, therefore, arguable fit within that common meaning.

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I would like to take a few minutes to briefly summarize the general regulatory framework that exists for supplements. But, first, I want to dispense with one misconception. FDA has ample statutory authority to regulate supplements. DSHEA did not free dietary supplements from federal oversight. The 1994 law did amend the act such that supplements are subject to a regulatory framework that is different from that which existed before the 1994 amendments and is somewhat different than the regulatory framework that applies to other foods, which I

will simply refer to as conventional foods, for lack of a better term.

In a general sense, the current regulatory framework is based on postmarketing oversight by the agency. There is generally no premarket review or approval by FDA needed before any dietary supplement may be marketed in the United States unless the product contains what the statute defines as a "new dietary ingredient" or it makes a claim that causes it to be subject to regulatory as a new drug or under the new-drug or under the health-claim provisions of the act.

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Products enter the marketplace based on a manufacturer's determination that its products are safe. Additionally, nothing in the statute requires that the firm share with us the information that is the basis upon which it has concluded that its product is safe. While the government does not have to determine that a product or an ingredient is safe prior to it being marketed, except for a new dietary ingredient, we have the responsibility to monitor the marketplace and develop evidence and information that would enable us to act against unsafe products that are identified postmarketing.

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So, to market a dietary supplement that includes

an animal-derived ingredient, a firm simply must comply with the basic rules that apply to marketing any other dietary supplement. First, it must insure that the product actually is a dietary supplement legally as defined in the act.

This means that, among other things, it must contain a "dietary ingredient" as I defined earlier, that it does not contain substances that are prohibited by'other sections of the act--for example, products that have previously been authorized for investigation as drugs or substances that have already been approved as drugs--and that it doesn't violate certain other exculsionary criteria--for example, that it is represented as a conventional food.

Second, the firm must insure that the product is safe, not only that it is safe within the meaning that it isn't inherently harmful but that it also is safe in other ways, that it is not contaminated with adulterants, it doesn't contain pathogenic microorganisms, and so on.

Third, it must label the product properly. The labeling, at a minimum, must include the disclosure of each ingredient in the product by its common or usual name meaning the dietary ingredient must be identified in terms that a typical consumer would immediately be able to figure out what the dietary ingredient is.

In practical terms, a minimum requirement for

animal-derived ingredients would be to identify the species of origin in the layman's term for the tissue being used. For example, one example--and I am not saying that everyone in the marketplace, by the way, is doing this to our satisfaction, but the term "bovine products" that use bovine testicular tissues, that would be the appropriate term rather than making up a name like orchic.

You can go down every tissue in the animal body and there is a sort of made-up name that has meaning to some part of the consuming public but perhaps not all.

[Slide.]

It is within this regulatory framework that dietary supplements may contain dietary ingredients that originate in animals. In general, there are four broad categories of animal-derived dietary ingredients that we are aware of in the marketplace, ingredients that simply are animal tissue, substances that have been extracted from an animal tissue of some type, ingredients that are not tissues out are from animals, things such as eggs, milk, colostrum, things of that nature.

Then, of course, there are ingredients from other animals. Bovine-derived ingredients are certainly not the only non-plant materials used in supplements. We are aware of everything from fish incrustation, birds, reptiles, fish, insects and everything else. So the issue of the risks

associated with animal-derived ingredients perhaps are not solely limited to those of bovine origin.

Keep in mind, however, that these are broad categories. Not everything in each of them would be eligible to be a dietary supplement, remembering that one of the defining requirements is, is an article that is the usual food or drink of man. So not everything that is of or comes out of an animal necessarily is part of the usual food or drink of man.

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A wide variety of animal tissues is used in supplements. These include glands such as the adrenal or pituitary. They can be organs, liver, brain, lung, what have you, and various other tissues such as velvet antler which we have heard about and blood.

As I have mentioned, animal-derived ingredients are not limited to bovine sources only. Supplements typically contain tissues from sheep, pigs and other mammals. Finally, as I also said, they also contain things such as milk, colostrum, eggs and their constituents and constituents that have been manipulated in the production so that the typical composition of those things has been manipulated, such as by vaccination or immunization of the animal it is coming from.

[Slide.]

Dietary supplements may also contain substances that were derived from an animal-sourced raw material. Some examples of these include glucosamine, which is typically obtained from bovine trachea, sphingolipids that have been isolated from animal neural tissue, and isolated proteins obtained from bovine spinal tissue and other substances and an array of metabolite from other tissues.

They also include specific proteins that have been isolated from bovine blood.

[Slide.]

As of this date, FDA has not promulgated regulations governing the use of animal-derived ingredients in dietary supplements. However, we have taken several actions intended to minimize the potential that bovine-derived ingredients from animals from BSE countries do not find their way into supplements.

First, FDA, since BSE was identified in Britain and the issue came to the forefront, has issued several Letters to the industry on the topic. The letters explain the agency's policy on the use of bovine-derived ingredients originating in BSE-positive countries; namely, that no such tissue may be used lawfully in a dietary supplement because tissues that may contain the causative agent of BSE in cattle presents a significant or unreasonable risk to consumers of the product and the product is, therefore,

adulterated within the meaning of the act.

The letter strongly advised firms using such ingredients that they should develop plans or processes that will insure that such tissues are not used. FDA has reissued those letters periodically as new developments have arisen and to keep the industry aware and focused on the issue.

The issue is specifically addressed also, the use of bovine-derived materials, in our compliance program that serves as the guidance to our inspectional components in the field offices. The compliance program contains guidance on priority issues that the agency wants addressed by its inspectors and requires inspectors to investigate, during routine inspections of supplement manufacturers, if they use bovine-derived ingredients, to identify the types of ingredients and to determine whether management has developed a program to insure that such ingredients don't derive from a BSE-positive country.

FDA has also issued an import alert that provides for the automatic detention and refusal of entry of any bulk material, bulk bovine-derived material, from any BSE country which, at this time, consists of all of the countries in Europe and then a few other countries scattered around the world in which BSE has been identified.

It also provides for the automatic detention,

without physical examination, of any shipment of any finished product, dietary supplement or other food, that contains a bovine-derived ingredient that originates in a BSE-positive country. Those finished products are refused entry unless the firm can provide documentary evidence that the tissues were sourced from animals that did not originate, reside or were slaughtered in a BSE-positive country.

[Slide.]

The information that we have on the use of animal-derived ingredients comes mainly from our import and domestic inspectional activities. First, the information from our domestic establishment inspection program suggests that the bulk of the bovine-derived material currently marketed in the U.S. is sourced either from the U.S. sources or from New Zealand, Australia and Argentina.

We are not aware of any sources of original material being originated from Europe. We also know that there is some export of U.S.-sourced materials abroad where it is processed and returned or is used as the raw material for the manufacturer of constituents; for example, U.S. beef tracheas exported to Spain and other countries in Europe where, then, the glucosamine or chondroitin is extracted out and then reexported to the United States for incorporation into foods.

The information we have, while limited, seems to indicate that most firms have a plan or a process in place to provide some degree of assurance that their ingredients are not originating in BSE countries.

[Slide.]

As I mentioned at the outset, the question, can FDA act against products, is yes. The statute provides a variety of means that the agency can act depending on the circumstances and the scientific information we have at hand. First, we can use our authority to refuse entry to imported products that are adulterated or that appear to be adulterated.

Second, the act provides for direct action against a particular product or class of products if it is adulterated within the meaning of one of the provisions of the acts that we enforce. Third, the statute provides FDA the authority to promulgate regulations to insure that products are safe or that they are manufactured in accordance with practices that would minimize the risks that they would pose.

That authority to issue good manufacturing practices was specifically conferred by DSHEA. The agency is developing proposed rules for that that, depending, may or may not be published soon--I mean, depending on what the incoming administration decides what is a priority.

Finally, the agency can always issue guidance--in the absence of regulations, can issue guidance and conduct manufacturer or consumer outreach to respond to particular safety issues in the interim while it undertakes either enforcement or rulemaking to put regulations in place.

Thank you.

[Applause. 1

DR. BROWN: Thank you very much, Dr. Moore. Would you be able to stay for a little bit?

DR. MOORE: Yes.

DR. BROWN: I would like Dr. Moore to stay and not ask him questions now, but have what I believe is a single presentation from the floor. Then we will open the issue to discussion.

Open Public Hearing

DR. FREAS: We are opening the open public hearing now. We have received one response to speak in this afternoon's open public hearing. That is from Dr. Scott Norton. If Dr. Norton is here, would you please come forward. You can either use the podium or the microphone, whichever is your choice.

DR. NORTON: I am Scott Norton and I am a physician in the Washington D.C. area. I am here speaking as a private citizen today.

I first became concerned about the presence of

tissues from ruminant animals in dietary supplements about six months ago and expressed my concern in a letter that was published in New England Journal of Medicine in July of Year 2000.

A couple of the products that I had looked at, and examined their labels, that raised these concerns I brought in right here. I will just read some of the organs that are found in one that is called Male Power. Deer antler, pancreas, orchic--despite what we just heard that the FDA prefers the term "testicular tissue" to be written on the labels, I have never seen a dietary supplement say "testicle." They always say "orchis" or "orchic" which may sound rather flowery to the etymologically impaired--thymus, adrenal, heart, lymph node, prostate, spleen and pituitary. There are actually seventeen organs in that particular product.

There is another product that is called Brain Nutrition that tells us that it is vitamins and minerals essential for important brain function. It does not mention that there is any glandulars on at least the bold print. But if you look at the small print on the back, we learn that it has brain extract and pituitary extract, raw, in there.

We know that many of the organs that can be found in the dietary supplements do fall in that list of organs

that are suspect for contamination with TSEs, the labels, in nearly all cases, identify neither the animal source nor the geographic location from which the organs were derived. I have seen one line that did specify from New Zealand cattle but no other manufacturer will list either the species or the geographic location.

The FDA's and the USDA's import alerts that we just learned about prohibit the use of these organs in foods, medicines and medical devices. But my reading of the alert, 17-04, suggests that DSHEA does allow some loopholes for these tissues to possible slip in.

I will just read from 17-04 that we heard. On the first page, it says that, "This alert does not establish any obligations on regulated entities." I love seeing legislation that starts out with that caveat.

Then it says, further, "The USDA regulations do not apply to bovine-derived materials intended for human consumption as finished dietary supplements." We also learn that the prohibition, or the import alert, is limited to bulk lots of these tissues, completed tissues, from BSE-derived countries. It does not mention if it is not a bulk import or.if it is raw materials rather than finished materials.

Further, we know that it is strongly recommended but not actually prohibited in the language here. So I have

not taken the assurances from that import alert that Dr. Yoore was trying to convey to us.

So, in sum, dietary supplements sold in the United States often contain ruminant tissues from undisclosed sources. Personally, I am rather squeamish and I don't think I would be eating prostate or testicle or pituitary, out I am also a little bit wary of consuming products with those glands, not just out of personal repugnance but simply out of a health concern.

So my question to the advisory committee is this; is my caution reasonable and, if it is, should we take further efforts to inform, or even protect, the American public from such exposure.

I was curious about Dr. Moore's remarks. I sensed two messages. One was the initial reassurance that FDA has the regulatory authority but then I also learned that it is the manufacturer's responsibility to provide those assurances, that the FDA doesn't actually inspect.

I think that the FDA commissioners from Harvey Wylie to David Kessler would say that that track record has proven itself.

Thank you very much.

[Applause.]

DR. BROWN: Thanks, Dr. Norton.

Committee Discussion

DR. BROWN: We now open a discussion, if there are no other public declarations, comments. We open the committee discussion. Before you go, Dr. Lurie, I wanted to ask, since Dr. Norton brought up three specific points on the--was it a legislative--was it 17-04? It had a number on it, whatever, the document from which he quoted.

The quotes seem to be in flat contradiction to what Dr. Moore suggested and I would like that ironed out in public. Somebody has misinterpreted or not interpreted far enough and I don't know who that is.

So, Dr. Moore, could you possibly respond to the specific sentences that were read? Thank you.

DR. MOORE: The import alert contains a guidance to FDA field personnel. It does not establish any requirements or create any rights or obligation. Those are standard disclaimers required under other administrative acts that govern the agency's regulatory thing. That is simply the agency cannot impose binding things on a regulated entity without doing notice and comment rulemaking.

Import alerts are not done under notice and comment rulemaking. So that is why that disclaimer is in there, to make that explicit. One has to read any legal document in its entirety. While the initial part, the charges, apply to bulk ingredients, when one goes to the

guidance section, it is explicit to the inspectional agencies that this applies also to finished products that contain specified risk material.

So it applies to bulk and finished even if the charges, as they are written on the opening page, use the word "bulk."

What was the third? You said there were 'three?

DR. NORTON: The wording that you quoted, and that I read also, just uses the phrases "recommended" and "strongly recommends," but it does not seem to have any absolute binding.

DR. MOORE: It doesn't because it is guidance. As I said, it is a guidance. For FDA to impose binding requirements on the industry, one must do notice and comment rulemaking. This is not notice and comment rulemaking. Therefore, it is a guidance. One cannot order someone to do--that is the very nature of the word "guidance."

DR. NORTON: I think it is that prospect of a loophole which we see, for example, just in the labeling of the testicle versus orchic, whether companies can, perhaps, use their own preferences for the labeling where they might be able to use their own preferences for the purchasing, again, in sort of contradistinction to the guidance.

DR. MOORE: A firm can always choose to ignore a law, a regulation or a guidance. It is a matter of FDA,

with the resources available to it, to pick and choose those things it is going to act on based on what poses, at that moment, the greatest public-health safety threats.

To the extent that firms are using labeling, identity statements to identify products that maybe wouldn't be the common or usual name the agency would prefer probably is not the type of violation of a regulation or act that the agency is going to devote resources to given that there are other issues that we would devote those resources to that have a direct public-health threat at that time.

So we are going to focus on safety, our resources on safety issues first. These more technical violations of the act are going to be dealt with on a somewhat lower priority.

DR. BROWN: I think, in general, what Dr. Norton is saying is what the committee has been aware of about other products, too. Guidance is the preferred, it would seem, mechanism or means by which the FDA seeks to insure safety. While it is true that one flaunts something that is suggested as opposed to something which is a law, at their own peril, I suggest that the peril to flaunt a law is substantially greater than the peril to flaunt a recommendation.

So I don't think there is an argument there. I have quite a lot to say about this subject, but, Dr. Lurie,

go ahead.

DR. LURIE: The debate, actually, reminds me a little bit of what the singer Tom Waits said about religion which was, "There are a lot of religions and they can't all be right. But they might just all be wrong."

I would like to thank Dr. Norton for what he has done here. I think it was extraordinarily brave of him to write this letter and I think that the interaction we have just seen is that, in fact, in this case, one religion is right. Dr. Norton is right here.

In fact, there is no teeth, whatsoever, to what the FDA can do in this area. He is absolutely right that guidances are liable to be flaunted and the experience of this very committee at our last, or next-to-last, meeting is that some of the regulated industries have done just that.

When the FDA passed its guidance with regard to sourcing of materials for injection, implantation and the like, to not source them from BSE countries in '93, we discovered that the regulated industries spent about seven years flaunting precisely that.

So there is no assurance here. I find, frankly, the assertion by FDA that they have "adequate regulatory authority" in this area is incredible.

It is incredible because there is no guarantee of safety except that which the self-interested manufacturer

might, itself, provide. There are no regulations on good manufacturing practices and there is certainly nothing on efficacy.

If that is what we call adequate regulatory authority, I just don't understand. Furthermore, if the issue is safety, the FDA knows well that it lost a case out west someplace of 34 people killed by Ephedra. Even 34 bodies, let alone the potential for illness about which Dr. Norton is concerned, were not enough to result in the change of the regulation of Ephedra.

So this is a tremendously worrying area. I agree that, at present, there may be no evidence of harm, but Dr. Norton has well indicated a real hole in the regulation not only here with respect to BSE but with regard to dietary supplements more generally.

DR. DETWILER: May I just, at least, correct one thing, and then I will tell you how you can--Dr. Norton nentioned about the USDA. There is no exemption for dietary supplements. There is for cosmetics. There is for gelatin. But there is no exemption for dietary supplements.

I will tell you one thing, though. In importation and what happens with importation, USDA, if it is bulk product, our regulations can keep out organs and tissues of ruminant origin. That is a given. If it is labeled with products of ruminant origin, we don't regulate end use. We

don't regulate end use.

Our regs is the material coming in. If it is Labeled as ruminant-origin coming in, then our system can pick it up and keep it out, with the exemptions of certain tissues going for cosmetics, but then CFSAN has a system in place there for cosmetics. Then gelatin, as this committee has looked at the issue of gelatin, those are our two exemptions.

The dietary supplements, since they are labeled with certain tissues, we can keep them out. However, if the Labeling is such where that is not apparent--that is what happened in the vaccine issue--we don't know--there is no way in our system, and maybe this is what you are alluding to--there is no way in our system to pick that up. We have no mechanism that says we know, the USDA knows, what is in there.

But there is no exemption in the 9 CFR for dietary supplements.

DR. NORTON: That's wonderful. I feel good to hear that but I just know that what I can obtain from the USDA's website it says, for example, since 1991, the USDA has prohibited the importation in the U.S. of certain tissues and organs from ruminants from countries where BSE exists.

Then it goes on to that 9 CFR 94.18. But then, at

the end of the paragraph, it says, "The USDA regulations do not apply to imports of bovine-derived materials intended for human consumption as either finished dietary-supplement products or for use as ingredients in dietary supplements."

DR. BROWN: The other point that could be made here is that something which--

DR. DETWILER: This is not the USDA's; is it?

DR. NORTON: That is the FDA's import alert 17-04 that cites the USDA.

DR. DETWILER: I just want to correct--this is not the USDA's.

DR. BROWN: Let me say something here and that is that it strikes me that if the FDA is depending on the USDA to be the primary stop gap, then that is punting the ball. If it is a question of the port authority stopping material that might be a risk in terms of its presence in dietary supplements, that is probably not the ideal solution.

It is nice that the USDA gets in on the act. It is a little disquieting to think that the USDA has the primary role in the act. I bring to the committee's attention just a case that we published as part of our iatrogenic disease paper a few months ago. I thought it would be instructive.

It is an anecdote, but it was the case of a woman in Massachusetts, several years ago, who died from CJD.

After the fact, it was discovered that she had been taking a dietary supplement for a year or two or three before--more than that, actually. She had been taking dietary supplements for years.

That is probably not uncommon either. I think probably it was, in fact, a case of sporadic CJD but it was a little worrisome to learn the ingredients of what she was taking. She was taking a half a gram of brain, of bovine origin, which, on the label, said was "imported," as though this was a merit.

It was not specified from what country it was imported but it was specified that it had been specially processed to retain all its natural purity and its potency. Here is a lady who is taking half a gram of brain for years, not knowing the origin of the brain, at a time when BSE was rampant.

As I say, there is no indication that the two were related. But it was a little troubling to realize that this had occurred. Brain is a favorite substance in many dietary supplements. And pituitary is a favorite substance in many dietary supplements. God knows what they do, in terms of improving human health. But I think there is a real consideration that they might do the reverse.

That is one of the reasons why I hoped, and now have gotten the opportunity, at least to bring into the

public domain certain concerns about these supplements.

MS. OLIVER: My name is Janice Oliver. I am from FDA's Center for Food Safety. I would just like to comment on a couple of things and a couple of comments that have been made.

When Bob was commenting on dietary-supplement regulation in terms of BSE coming in from countries and how we regulate it coming from other countries, he was not commenting on DSHEA and its regulatory authority all the way across the board. That would have taken much longer. He had a very small presentation on it.

The import alerts that we have are guidances to our field. The primary focus, because it is easier to do, is looking at bovine ingredients that might be coming in from BSE countries. That is in the bulk.

There are two ways for doing that. One is USDA, and some of it is done through USDA. The other is that companies, through Customs, have to notify FDA of any food products or other products that are coming in, and so we get notified. Our inspectors, then, are notified of those things and automatically detain them. They are not allowed into the country.

That is what the import alert does. It is automatic for notifying the investigators and inspectors. The products are also included in there that are dietary

supplements if they come from BSE-originated countries and have bovine ingredients.

As you said, there are a number of products that are on the market, and I think two were pointed out, that don't have the source. They should have the source on them. They are not required to have the country of origin for bovine ingredients or for any ingredients on the list. It is only when they come in that they know that or when we go to the inspections of establishments to find out where do they get their ingredients and what do they get.

I just wanted to clarify those things that you were talking about before. That is an import alert which is not a regulation. There are two parts to it. The first part you read was very clear. I looked at it again this morning and it is very clear dealing with the bulk ingredients.

The second part is, basically, saying, if you get dietary ingredients in, or a dietary supplement from, a country that has BSE, then you are to call the Center for Foods. There is a contact in there. It basically ends up being an automatic detention. That is what happens. They are detained.

DR. NELSON: But the number of countries that are endemic for BSE are changing.

MS. OLIVER: Yes.

DR. NELSON: How quickly--I mean, you must always be behind the risk, given the BSE situation?

MS. OLIVER: It originally said U.K. It has been updated several times as it has been--I don't have the list of countries. Bob has it. It includes all of Europe and it includes a number of other countries, so it has been updated since additional information has come in. That is what has happened. It includes the new BSE countries as the information comes from USDA.

DR. NELSON: Why is there no requirement that it is on the label? That doesn't make sense--where it comes from?

MS. OLIVER: There isn't any. I can't answer why, but there is no requirement that it be on the label where the specific ingredients come from.

DR. BROWN: Linda, would it be okay to share a couple of--information about possible loopholes to this from last week's meeting, or not?

DR. DETWILER: The one thing that I do--there are loopholes. I am not going to say that--but I don't want people to be misled. If it is brought to our attention, we do have the regulatory authority to keep it out, other than the exemptions that I said. So that is where I really wanted to make it clear. I'm sorry. I get defensive about that.

But there is nothing in our regs that exempts dietary supplements per se, if it has those. But, again, we have to know about it. See; we have to know what is on there in order to prevent that. I think that is where we don't have--like, for animal vaccines; that is one thing that comes under our jurisdiction: So we do require, just like the FDA, for human vaccines, the list of things and what is in there.

DR. BROW-N: Maybe I could just ask you what is the way station for determining what, in fact, is in a package or a bulk or anything. The first people that see it, when it comes into this country, I think you said were the Customs and Immigration people. They are responsible for categorizing it according to what documentation they have.

DR. DETWILER: That's correct; yes.

DR. BROWN: One of the categories is miscellaneous.

DR. DETWILER: This was something Bob probably could address because that is something that he brought up yesterday. I am not sure if that applied just to the products. Maybe he could clarify that.

DR. BROWN: Even before he does, you remember the wonderful story that was told about a bulk shipment of a material that was labeled pesticide. I am just recounting this to indicate what can happen. An alert Customs and

Immigration officer looked at the size of this thing and said, "That is an awful big package for pesticide."

He opened it and it turned out to be meat and bonemeal. It was meat and bonemeal because it was going to be spread on ground to prevent grazing by deer who hate the smell of meat and bonemeal. That is the kind of thing that probably doesn't happen but very rarely, but it can happen.

If we are depending on sawy Customs and Immigration officers as our first line of defense, it is a very nice line of defense to have but it seems to me there ought to be one or two closer to the FDA.

DR. DETWILER: That was a combination of Customs and USDA. Just to give our guy credit.

MS. OLIVER: May I say one more thing--Janice Oliver--on the closer--and on the thing that you were talking about where something is brought in under another name. Over this past year, there was a initiative, a presidential initiative, in which FDA and Customs basically put into place a plan and the development of additional rules and additional safeguards really to target bad actors, which is really what you are targeting about.

There has been additional surveillance. There is additional secured storage, additional civil money penalties. There are a number of things to go with that. I am just acknowledging that that can happen and we are

putting into place, as has Customs, additional things to try to have that not happen. That is different than when things are identified when they came in and they are identified to customs and rightly identified and we do something with them. That is a second part of the story.

DR. BROWN: The use of blocking imports is certainly one approach to maintaining the safety of the product. But another approach, of course, is requiring the producers of the product to document, in a satisfactory way, the authenticity of what they are telling you.

My understanding is that the FDA really cannot do that under the present law, not in the way they can do it with other products including other food products; that is, you ask a manufacturer, you suggest it to a manufacturer, you guide the manufacturer, say, "It would be awfully good if you did this and we certainly recommend that you do do it; do you do it?" and the manufacturer sends back a letter and says, "Yes."

You put the letter in a file. I would be much more assured if I knew that there was some mechanism in place that was actually used by the FDA to authenticate and document the truthfulness of this industry's response to your guidance.

It just seems to me that you ought to hold--I can't say that you ought to hold, because maybe you don't

have the authority to hold, but it just seems to me a logical thing to hold this industry to the same standards of safety that you hold every other industry to.

DR. CLIVER: A couple of impressions. First of all, it was clear to me when the dietary supplements law was passed that it was the intent of Congress to make it as difficult as possible for FDA to do the things that they had always done with drugs, for example; no proof of efficacy, safety is sort an ephemeral concept there. Beyond that, though, as far as division of responsibilities among the various agencies is concerned, it gets very difficult, at the federal level especially, to build in redundancy.

The fact that USDA APHIS has a specific responsibility for what comes in at a port that may be of animal origin or that might have agents of animal or plant disease, yeah; we could look for backups on that. But it is not our place to reinvent government. This is the way government works.

There is an inauguration going to happen tomorrow. We may find government being reinvented on very short notice here but I bet that some of the things we would most like to see happen are not going to.

So we are in a situation where we are working within a system and we need to provide as good guidance that may have some scientific basis, as we can. I think that is

what we are being asked to do. Personally, I wonder about calling something an herbal supplement that has all these animal products in it. That strikes me as clearly mislabeling. But, beyond that, just the fact that we don't explicitly outlaw--including eye of newt or wing of bat doesn't necessarily mean that the public isn't being protected with reasonable certainty.

DR. BROWN: You can. I would add only to that--I think you are absolutely right--that we also have a little part in reinventing government. And that is what we are doing.

DR. MOORE: I would address two issues. What we can do is to limit the availability or to take action against a substance. We can do--with the authority that Congress has given us in the statute. If the statutory authority doesn't exist, FDA, as a regulatory agency, can't dub itself with that authority. That is a legislative fix to the extent that you may not be perfectly satisfied with some of the elements in our statutes. It is Congress that is the appropriate part of the federal government that can change that law, not FDA.

The second is regarding the authority for identity and to document source. Clearly, our view is that authority exists. It is authority that exists probably in the parts of the statute that gives us the legal authority to impose

good manufacturing practices.

To the extent of what types of records we can require the industry to keep, whether or not we have access to those records, are legal questions that are way beyond the time we have here.

We have been working on good manufacturing practices. They are written. They are at the Office of Management and Budget. When, if or what they do with them is out of our hands. We have gone as far, under the Administrative Procedures Act, as we can go at this point to address these issues. It is a matter, now, of, once that proposal is released for publication in the Federal Register and the rulemaking process moving on.

DR. BROWN: I don't want anybody in the room to think that I, personally, am putting the FDA on the defensive. I think the FDA, as you say, is doing about as much as it can. What I had hoped would be to put on the public record a sentiment which desires more. I think probably the FDA feels the same way.

DR. PRUSINER: I wonder if we could just take a few minutes--I don't want to drag this out because it is probably not--it may not be what you think is appropriate but I think it is appropriate in the sense that it is really illustrative. I would like to see the FDA comment on this.

If we take a specific dietary supplement that is

sold. Let's just take one. What we have heard about are these sort of lots of stuff in one. Let's talk about melatonin for a moment because here is something that large numbers of people are taking. There are books that are written about this. This is a real fad.

In many European countries, you can't even buy it, for whatever reasons; it is not clear to me. In the United States, it is freely available. I can tell you that I think the stuff works. It does good things for jet lag and, after trying it a few times and becoming convinced it works, then someone says to me one day, "You know, this stuff is all extracted from bovine pituitaries."

I threw it all out. So the next thing I do is I start to investigate where does the stuff come from. Then I am told by the manufacturers in the United States, at least one of them, that it is all synthetic. Then, if you look on the labels, it says, "HPLC-analyzed," whatever this means.

I would like to know if we have any information about something like this as a specific instance of something where we--everyone on this committee, I am sure, would not want to have melatonin extracted from bovine pituitaries whether it is in the United States or whether it is from Europe, especially from Europe, flowing into the consumer market. Tons of this stuff is being purchased and used.

DR. BROWN: Let's follow up with that specific example. You say the label or the manufacturers say it is synthetic. I suppose a synthetic substance could be imported from Europe. So suppose we have this example, melatonin, said to be synthetic, imported from Europe. Is there any documentation to indicate that the synthetic is really synthetic? Is it manufactured somewhere in a factory?

Is there any validation of what is on a label or do you simply trust what is on the label and what the manufacturer says.

DR. BOLTON: I think that is an excellent question. I think a recent example of that goes back the term "organic" in terms of organic foods. Is there a definition of synthetic or natural that is used and accepted by the FDA or any regulatory agency that has actual meaning?

DR. PRUSINER: This gets amplified in Dr. Moore's presentation about, let's say, glucosamine. We have U.S. materials going to Spain, being extracted in Spain, maybe extracted in a plant that is extracting glucosamine from European animals. Then it is cleaned by whatever process they decide to clean it by and then they start extracting materials from the U.S., and they return these to the U.S.,

Especially in the case of the prions which are so difficult to inactivate, how good is the cleaning process?

DR. BOLTON: I have an additional question about that. What is the assurance that additional locally sourced tracheas are not added into that manufacturing process, thus boosting the yield, if you will, but being returned to the U.S. as being produced from U.S.-sourced raw material?

DR. McCURDY: Are there'data to indicate how many grams, or whatever, of infected brain are likely to infect an organism, either animal or man, when taken orally?

DR. BROWN: If I am not mistaken, and I can be corrected, I think a half a gram is enough in a cow, orally; in other words, one good dietary-supplement pill.

DR. McCURDY: What I am driving at is the question we are asked is really not do we wish to regulate these things coming in. I think the statements about difficulties in regulating things in the future or near future for new regulations were probably accurate.

But I think that we could exhibit some quite reasonable concern about blood donors who are taking dietary supplements that contain a certain amount of unspecified-origin brain, brain-related, brain and pituitary material. If they have done this for more than a sniff or something like that, then, perhaps, they should be deferred as blood donors.

That is probably worse than spending six months in the U.K.

DR. BROWN: That is exactly right. I think that is why the discussion has apparently been on things that are not directly related to these questions because, in order to think about deferrals for blood donors who are taking dietary supplements with things like bovine brain in them, it is very important that we know that those products are safe.

I think we have heard enough to suggest that they may not be.

DR. McCURDY: There is one other item that needs to be considered and that is what proportion of blood donors are doing this; that is, how many blood donors would you lose, and I don't know what the demographics--there is fairly good information on the demography of blood donors. I have no idea what the demography of people who take these supplements is. Maybe they are old men like me and aren't going to be blood donors anymore.

DR. BROWN: The wording of the question is not as demanding as the wording of other deferral questions; that is, the question here is "consider recommending." We are not even recommending at this point. We are saying to the FDA, please think about this. It is worth thinking about.

DR. DETWILER: One point about brain from Europe, and Jean Philippe is still here, those are considered specified risk material and it is not correct to be

ealing with that data and these issues and the concern in a ore dedicated fashion.

I think what we know now is that we are concerned bout this, that we don't think it is as regulated as it hould be but what I am not sure about is, in fact, how much ovine central-nervous-system product really is on the helves at the moment or has been over the last five years.

I think we need to know that. Now, maybe we can't 'igure it out exactly, but I think we could change the necdote. We could figure out where melatonin comes from nd get that data and have it returned to committee because think that is a very important piece of information in rder to guide us in our actions and the level of our oncern.

DR. BROWN: I can tell you from having visited a hop locally that sells nutritional supplements that about a uarter of the nutritional supplements on the shelves ontained brain or pituitary. There is a lot of brain out here, number one.

The other matter is that we do already ban the importation, for example, of brain. And brain is being ingested.

DR. ROOS: But remember, Paul, there are plenty of people in the United States who have brain regularly and want to do that.

DR. BROWN: But we don't import it. We can't import it from Europe.

DR. ROOS: The importation is, yes, to me, the issue. How much of what you see on the shelf is imported central nervous system.

DR. BROWN: What I am trying to say, Ray, is that we did not require a systematic epidemiologic study of CJD in people who eat imported brain from Europe before banning its import. We just didn't do it. To require that would set a different standard for nutritional supplements than it does for brain--and I use brain because it is orally ingested. We obviously don't do it for blood.

I am not arguing with you in terms of yes, it would be nice to have this data, but we have certainly acted without--

DR. ROOS: No; there are two issues. One is whether one should ban it, and I agree with it. And the other is should one be concerned about individuals who have ingested it and who have known dietary histories that might be more worrisome than spending six months in U.K. It is that issue which really relates to deferral practices here by the FDA that I think we need a little bit more data on.

I agree with the ban.

DR. BROWN: One source of that data, and I don't think anybody is here from the European CJD Surveillance--

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DR. BROWN: The wording of the question is not as demanding as the wording of other deferral questions; that is, the question here is "consider recommending." We are not even recommending at this point. We are saying to the FDA, please think about this. It is worth thinking about.

DR. DETWILER: One point about brain from Europe, and Jean Philippe is still here, those are considered specified risk material and it is not correct to be

ıcinerated; correct? Or destroyed? Brain and spinal cord
ıd other high-risk tissues in Europe?

DR. NORTON: In tomorrow morning's British Medical
ɔurnal, which has appeared on-line today, there is an
rticle called "U.S. Takes Precautions against BSE." One
aragraph says, "Even though the U.S. and U.K. governments
an the practice of feeding cattle products to cows, in the
arly 1990s, some U.K. renderers continued to manufacture
nd ship contaminated meat and bonemeal around the world.
ritish export statistics show that thirty-seven tons of
.eal made from offal was sent to the United States in 1997,
'ell after the U.S. government banned imports of such risky
ıeat. The ultimate use of these imports has not been
.dentified."

That will appear tomorrow morning.

DR. DETWILER: That actually was in The New York
:imes. That is a direct quote out of The New York Times
ırticle. We called the reporter on that. That statement,
:he thirty-seven tons, was taken out of the U.S.
Geographical BSE Risk Assessment. What they didn't put in
:here, in the statement, was the remainder of the GBR is at
:hat time, the big labeling for that category in the U.K.,
ɔecause it was illegal for them to ship it to us from their
ɔwn regs. It is illegal for us to get that.

We did go and try and trace that so that wasn't

correct on there. But we did import feather meal out of the U.K. at that time, but the big labeling, and it is right in the GBR, says that there was a big catch-all category from that.

DR. PRUSINER: Can you translate that?

DR. DETWILER: I'm sorry; it has been a long two days. They have a category--this is from their export statistics. It is flowers, meals, and what not. The notes on there to say that it was illegal there. Britain was not shipping that product out. It was illegal to send it into the U.S., however, it could contain--that category was other; flowers and poultry and non-mammalian protein.

At that time, it was still okay to import to the United States poultry and feather meal which we had done. We had some shipments.

DR. ROOS: I guess we have heard about the legal aspects of this from the FDA and the ingredients of two products which were vaguely noted and concern about melatonin, and your anecdotal report, Paul. But all of these are anecdotal. I would like to say what we really need is data, if we can get it.

In other words, how often has bovine central-nervous-system product come in or how often is it coming in now. Is that able to be identified or known even by figuring out what is bovine product by analysis and then,

dealing with that data and these issues and the concern in a nore dedicated fashion.

I think what we know now is that we are concerned about this, that we don't think it is as regulated as it should be but what I am not sure about is, in fact, how much bovine central-nervous-system product really is on the shelves at the moment or has been over the last five years.

I think we need to know that. Now, maybe we can't figure it out exactly, but I think we could change the anecdote. We could figure out where melatonin comes from and get that data and have it returned to committee because I think that is a very important piece of information in order to guide us in our actions and the level of our concern.

DR. BROWN: I can tell you from having visited a shop locally that sells nutritional supplements that about a quarter of the nutritional supplements on the shelves contained brain or pituitary. There is a lot of brain out there, number one.

The other matter is that we do already ban the importation, for example, of brain. And brain is being ingested.

DR. ROOS: But remember, Paul, there are plenty of people in the United States who have brain regularly and want to do that.

DR. BROWN: But we don't import it. We can't import it from Europe.

DR. ROOS: The importation is, yes, to me, the issue. How much of what you see on the shelf is imported central nervous system.

DR. BROWN: What I am trying to say, Ray, is that we did not require a systematic epidemiologic study of CJD in people who eat imported brain from Europe before banning its import. We just didn't do it. To require that would set a different standard for nutritional supplements than it does for brain--and I use brain because it is orally ingested. We obviously don't do it for blood.

I am not arguing with you in terms of yes, it would be nice to have this data, but we have certainly acted without--

DR. ROOS: No; there are two issues. One is whether one should ban it, and I agree with it. And the other is should one be concerned about individuals who have ingested it and who have known dietary histories that might be more worrisome than spending six months in U.K. It is that issue which really relates to deferral practices here by the FDA that I think we need a little bit more data on.

I agree with the ban.

DR. BROWN: One source of that data, and I don't think anybody is here from the European CJD Surveillance--

they have about, I don't know, 500, 600, 700, maybe 1000 cases of CJD for which extensive dietary histories were taken throughout Europe. I am pretty sure one of the questions was dietary supplements.

That would just be one source of information. It wouldn't be definitive but at least it might give an idea of what you are talking about; that is, is there any relationship between dietary supplements--on the other hand, they probably couldn't ask if the people knew what the dietary supplements contained.

They might have been arrow root instead of brain. So it probably is not information that is available anywhere in the world.

DR. BURKE: I don't know what the word "banned" means yet because we have heard several interpretations of what a ban is. If we knew today that somebody was importing, still, from the United Kingdom brain that was going into nutritional supplements and it wasn't being picked up at importation, do either the FDA or the USDA have any powers to do anything about that?

DR. DETWILER: Yes. If you found something that came in, we would have the power to go back, if we had found something on the shelf, to go back. The cosmetics or the gelatin; those are the only ones we don't--to go back and trace that back, to take action.

DR. BURKE: What would be the actions that would be possible?

DR. DETWILER: It depends on the circumstance. If it was brought in versus administrative, and that is the most likely action, versus a criminal action.

DR. BURKE: So there is some authority there in existence today.

DR. LURIE: That is if you knew.

DR. BROWN: But it is interesting that it is USDA authority.

DR. DETWILER: Right. That is it exactly, if you knew. But that was the point. You said if we found it; right?

DR. BURKE: That was the question

DR. LURIE: But the point is you might not know.

DR. DETWILER: Absolutely.

MS. OLIVER: FDA has authority, too, to take it off the market. We have it on an import alert which, basically says we deny entry on certain charges. If it came into the country, we would--we would have to know about it, obviously. We would seize it. We would ask for it to be recalled. We would do those things. We are talking about the BSE.

DR. BOLTON: What obligation is there of the manufacturer to document and inform the FDA or the USDA of

the source of the raw materials in these products? Is there any obligation?

DR. DETWILER: That is where I said before, those things for human use, other than meat which comes under the meat inspection, but for human use, those things don't come under our authority to document what is in them.

DR. BOLTON: So if I am a manufacturer of a supplement and I have a bottle on the shelf that does not say where the raw materials come from, and I don't have to document that and I don't have to inform anybody, how will you find out?

MS. OLIVER: There are two things that we do. It is not foolproof, but I can answer that question for how we find out. One is on imported products that come in, if it has a bovine ingredient, we will, from a BSE country--it is coming from a BSE country--we will detain it and we will require that they provide us the source of that information, as long as we know about it.

If we go on inspections and it is one of the things that Bob was saying, one of the things that we have our inspectors do during inspections of dietary-supplement manufacturers is, if a bovine ingredient is being used by the firm, we ask that they find out the source of the bovine ingredient and where it is coming from.

So they determine that. But the manufacturer

does--

DR. BROWN: Would you run that by again, please, one more time?

MS. OLIVER: Yes. The manufacturer--

DR. BROWN: The whole of that sentence.

MS. OLIVER: Okay. Going from the imports. On the imported products, we have a directive, an import alert, to our field that when the product comes in, and we have to be notified of entry of dietary supplements, whether it be in bulk or whether it be as a finished product. If we are notified of it, and USDA is also one criteria for the bulk ingredients--if we are notified, we are to detain them which is denying entry. We do not allow it entry from a BSE country.

If it is an importer and it is from a BSE country and it has multiple ingredients on it, some of which are bovine origins, we will ask the importer to determine for us where that has come from or we will deny it entry until then.

If, during an inspection, and I say during an inspection because we do not require it of everybody, during our inspections of dietary-supplement manufacturers, one of the items that we have for the inspectors to check during the inspections is if bovine ingredients are used in the dietary supplements, to check the source. They are checking

to see if it has come from a BSE country. That is what they are doing.

Now, we do not inspect every country regularly, if you come back to ask what we do. But that is what we do during the inspection.

DR. BROWN: What if Spain, or let's say what if a manufacturer in this country using bovine brains, say, has it processed in Spain. Perhaps it comes from Spain. And then they send it to Canada. And then Canada runs it across the country on a train?

MS. OLIVER: That was one of the things that Bob Moore talked about earlier. He had a number of things that he talked about in the slides and what we have found out in inspecting dietary-supplement manufacturers is that some products are shipped either from the United States, from Canada, somewhere else to be further processed and that we need to further look into what controls are needed and do some additional work in that.

DR. BROWN: I agree, but--go ahead.

DR. BOLTON: So, for example, if a company was using a bovine brain extract that was imported from Morocco, say, there is no guarantee that that material might not have actually originated in the United Kingdom, the brains being sent to Morocco, ground into a paste, bottled and shipped from Morocco. Here it would look like they came from

Morocco.

MS. OLIVER: The information we would have is the source information that was either provided by the importer or was provided by the processor.

DR. BROWN: I don't think the committee is expecting the FDA to act as policemen and to detect out-and-out fraud, dishonesty,

MS. OLIVER: Right.

DR. BROWN: We know that, but what I am getting at and what I think some of the other members of the committee are getting at, is that there is a spongy quality to the precautions.

MS. OLIVER: All I am trying to do is clarify what we have and what we don't have. I am not trying to say it is a fail-safe thing. We did not bring everyone here from the Office of Dietary Supplements or otherwise to provide all the information for some of the questions that you are asking.

We provided information on looking at the controls for BSE that are coming into the country. We did go further. One of the things we are going to do after this committee is go back and look at, again, what additional things besides what we are doing do we need to do

DR. LURIE: The two kinds of authority you mentioned were, one, in effect, the labeling which you have

already shown can be eluded, at least in principle, by transshipment. The second was inspection. I guess my question to you is how many of these dietary-supplement manufacturer plants have you actually inspected?

What I am struck by is we are worried about the definition of organic--was that the expression? I am worried about the definition of the word "milligram" because the variation in the amount of these substances from drug to drug, from batch to batch, is enormous as it is.

So what kinds of inspections, really, are you doing and what fraction of places have been inspected?

MS. OLIVER: I can't give you that. The people who would give you that information are not here with me today, that would have the information. We can certain provide that later. I just don't have it offhand.

DR. DETWILER: I think one of the points here, and I heard it a little from FDA, but just from the government agencies, I think it is really important to take away--as Dr. Cliver said, we can only do what the authority of Congress gives us to do. YOU can even see with the Vermont sheep, that is exactly why we are in court because someone is challenging that we don't have the authority to do it.

I think we are all facing that, that we get challenged more and more. And so that is one thing that I think is important take-home for the committee.

DR. BROWN: I don't think anybody disagrees with lat.

DR. CLIVER: I was just going to say, apropos of einventing government, though, it is all a matter of rigor. Some years ago, I wrote a piece proposing that FDA and USDA get together and ban ingredients from the U.S. food supply. ou may have missed it. It was published in the Journal of rreproducible Results. But, all the same, I think that ould get the job done.

DR. BROWN: Shucks.

DR. ROOS: I think one aspect that will fuel FDA's bility to act and give it authority is if we know how well, r poorly, things presently ran. In other words, for omething like Stan's melatonin, or some of the drugs we aw--in other words, if, in fact, we could demonstrate that ovine central nervous system was, in fact, on the shelf, erhaps that would drive home the message here and the concern and also provide some of the authority as well.

DR. BROWN: You have seen two bottles. It is out here, Ray. I don't know how many bottles we have to bring n.

DR. ROOS: We know that it is central-nervous-system tissue. But is that from U.K. or local?

DR. BROWN: Ah; from the U.K. That is another issue.

DR. ROOS: Anybody can get central nervous system locally here and it is up to people if they want to take it or not.

DR. BROWN: Right; but a lot of the discussion surrounded the idea that it is labeled bovine. Maybe the country of origin isn't specified and maybe it could come from the U.K. and it is a hell of a thing to try and figure out, under present law and authority, what the truth of those statements is.

DR. ROOS: I think it is a good epidemiological study.

DR. BROWN: I would also respond to Linda, just as I responded to Dr. Cliver, if somebody doesn't make a noise, nothing happens. So just to say we can only do what we can do and not try to do more doesn't fly with me.

DR. DETWILER: That was not my point I was making. It was the point to get that on the record again as the emphasis here that that is some of the--

DR. BROWN: Right.

DR. DETWILER: That was not my point to give that as an excuse to all of us. I have actually come here and asked the committee to make recommendations to help us get support.

DR. BOLTON: I think it is worth putting on the record that at least I, personally, as a committee member,

believe that the USDA and the FDA do need the authority to do more. If it is Congress that needs to act, then they should look into it.

DR. NELSON: If we voted yes to this question, wouldn't that send a message that this is an area that has been neglected or not adequately dealt with, or spongy or whatever, that the FDA needs to look into without saying--

DR. BROWN: Certainly together with the transcript, I think that is true.

DR. NELSON: I think the Congress might get the message if we found out that half of our blood donors are taking dietary supplements and we don't know where the hell we are coming from.

DR. McCURDY: That was going to be my point. I think we could probably bring this to closure by simply making a recommendation or indicating that we are deeply concerned about the likelihood that blood donors would be taking orally sufficient brain-derived material to be of potential risk for CJD.

DR. BROWN: One way to begin to bring it to closure is to go ahead and vote on question 1, which we can do, now, I think.

DR. DAVEY: Just one last comment, along with what Paul has said, I think that I would agree with Dr. Roos that we need to get data on the supplements. Whatever we can get

that makes sense at this point would be useful for committee, I think.

We also need data on blood donors in terms of what they are taking and how much of it before we can even begin to address the problem because it is going to be a huge percentage of donors. Before we move on to that, which we are not, we have to have those data in hand.

DR. BROWN: Right. I want to remind the committee and reread the question; should the FDA be sufficiently concerned about the suitability of any blood donors potentially exposed to TSE agents of animals to consider recommending deferral. We are not voting on recommending deferral. We are voting on considering it.

DR. BELAY: Why don't we take out that last part of the sentence?

DR. BROWN: Because I think it is an important part of the sentence to leave in. That's why.

DR. BELAY: I agree with what Dr. Roos is saying. This is because we don't know how many donors--

DR. BROWN: How much of the sentence do you want to take out?

DR. BELAY: Just the last part.

DR. BROWN: That could be two-thirds, or two words.

DR. BELAY: No, no; the part which starts with "to

consider recommending deferral."

DR. BROWN: Should the FDA be sufficiently concerned about the suitability of any blood donors potentially exposed to TSE agents of animals?

DR. BELAY: Yes.

DR. BROWN: Sufficiently concerned to do what? To consider recommending deferral.

DR. McCURDY: I think that is accurate.

DR. BROWN: I think we are going to vote on the question as written.

DR. McCURDY: Yes.

DR. ROOS: It is not recommending deferral. It is just considering it. So I think it is a little spongy.

DR. BROWN: Ray?

DR. ROOS: I will give it a yes.

DR. DETWILER: I just want this broad thing because sheep scrapie is not known to--I don't know; would that--I guess the FDA can sort that out; right? Because we have already had that.

DR. FREAS: Is that a yes or a no?

DR. DETWILER: That is a yes.

DR. EWENSTEIN: Yes.

DR. BURKE: Yes, but it seems that the FDA is already considering it.

DR. McCURDY: Yes.

DR. FREAS: Is Dr. Gaylor here? No?

DR. NELSON: Yes.

DR. BOLTON: Yes.

DR. BROWN: Yes.

DR. BELAY: Yes.

DR. CLIVER: Yes.

DR. LURIE: Yes.

DR. WILLIAMS: Yes, but with the same caveats about U.S.-derived TSEs.

DR. PRUSINER: Yes.

DR. FREAS: That was thirteen yes votes.

DR. BROWN: Thirteen to zero. The second question; if so, which animal TSE agents present or imported into the USA, what types of product and intensity--has that been crossed out of the final--should be or imported into. Is that right, Dave? Is Dave still here? That didn't get revised in time?

DR. ASHER: Give us a second here.

DR. BROWN: Or accidentally imported; right? If so, which animal TSE agents present in the U.S.A, or accidentally imported, what types of product and what intensity of the exposure should be of concern?

I don't know if any of us can talk about intensity of exposure, but we could probably make some comment about what types of product, which animal TSE agents present in

what types of product.

Beth, you were concerned about that and so were youI Linda. You were saying that you don't think scrapie is one such TSE. We would all agree about that.

DR. DETWILER: Yes; it is thinking this whole big thing, with the thing of possible exposure if you eat sheep or what not, here, that you have a huge--

DR. BROWN: No, no; I agree. There is 250 years, at least, of epidemiologic evidence that scrapie does not pose a direct human pathogenic risk. There is direct evidence in spades that BSE does, and there is the potential for something like elk velvet antlers, too. We just have no idea. We don't know.

But if the committee has any other suggestions about--those are the only animal TSEs I am aware of. Mink don't seem to be present in nutritional supplements--that I know of.

DR. BELAY: Dr. Brown, the only animal TSE that I would be concerned about under question 2 would be BSE.

DR. BROWN: That is, obviously, the major concern.

DR. BELAY: I would **say** the only concern that I would have.

DR. NELSON: But, actually, which countries are at **risk is changing and I am not sure how well** even **regulations are keeping up with the change.**

DR. ROOS: Why shouldn't we be concerned about ıronic wasting disease? We basically discussed that we had ery little information about it, so it is certainly of potential concern.

DR. BROWN: I agree. For the present, we have no dea if it is a concern or not, but we all know that BSE is concern. So it seems to me a logical answer to question 2 ould be BSE in BSE countries. That is the agent and that s the area.

DR. NELSON: In neural tissue? Which tissue?

DR. BROWN: It doesn't say which tissue. Is that new one?

DR. BOLTON: It says what types of product. I eard the thinking on scrapie. I, personally, would not eat heep brain.

DR. NELSON: No; I wouldn't either.

DR. BOLTON: 'Even if it was from the U.S. in a scrapie-free flock, I probably would not. I would be a .ittle concerned about a dietary supplement that was made rom CNS tissue of sheep or bovines, even if they were sourced in the U.S.

DR. BELAY: But the question doesn't address whether or not we should consume--or consumption of brain. The question specifically mentions whether or not we should consider deferring donors who have consumed this product.

DR. BOLTON: I think this question asks which animal TSE agents present in the U.S. or accidentally ported into the U.S., what types of product and what ntensity of exposure should be of concern.

DR. BELAY: It is related to question No. 1. It annot be taken without question 1.

DR. BROWN: So what we are mainly concerned about s BSE brain.

DR. BELAY: That's correct.

DR. BROWN: That would be at the top of the list. nd possibly brain, period, as a kind of unattractive utrient.

DR. LURIE: Paul, maybe I am, again, confused bout these questions, but I understood, when I looked at hese questions, that 1 and 2 actually applied to these hree specific products that were identified for us under ssue 4 which were products derived from deer and elk, the 'ermont sheep and the dietary supplements.

DR. BROWN: No, no; my reading is that this is a strictly independent issue. Issue 4 has nothing to do with issue 3.

DR. LURIE: No, no, no; that was issue 4. That is issue 4. It says, "the following will be discussed."

DR. BROWN: Oh; the TSE agents. Right

DR. LURIE: Yes.

DR. BROWN: So we have the full basket of agents to think about but we don't have to make it global; that is, we don't have to say, "Yes; it has to be mink encephalopathy, BSE and scrapie." We can pick and choose.

DR. LURIE: My point is I thought we only had to choose from these three. That is the way I understood it.

DR. BROWN: It is animal TSE agents. That is a global, any animal TSE agent. But there are not many.

DR. NELSON: Three is ruminant-derived tissues. So that would be the BSE.

DR. EWENSTEIN: I take the point that is being made. I think the FDA is directing us at a couple of very specific points. I think it is fair to include, as our chief concern, these dietary supplements which I find astounding in terms of their risk given the fact that we saw, even the data that Linda presented, if you want to give a sheep BSE, you give them a half a gram. That is what you were giving every day to that patient you took a look at.

DR. BROWN: No; I did not give that. No, no.

DR. EWENSTEIN: That is what "one" was giving to that patient that you were asked to look at. But I think there are specific questions. In other words, if someone is heavily involved in this industry, if they eat deer or elk meat, if they had cheese made from these Vermont sheep, I think those are questions that we should address, even if

the answer is we don't want to have an answer right now to the FDA.

I think the FDA is asking us to address those specific risks.

DR. ASHER: Yes; it would be helpful if you would address exposures to chronic wasting disease, the Vermont sheep and dietary supplements. You already know that we are concerned about all exposures to BSE agent. The only concern is whether there are ways in which it can enter the United States through these products.

You would be welcome to address scrapie but that was already addressed a year and a half ago at some length and no concern was expressed about dietary exposures, of which we have a very long and reassuring experience.

DR. BROWN: Is the committee agreed that BSE is the prime villain as a potential danger?

DR. BOLTON: Can we include in that the possibility that undifferentiated scrapie in sheep, at this time, may be BSE? It is going to take some time, I guess, to document whether that is, in fact, scrapie in those sheep or whether that is BSE in sheep.

At that time, does that become BSE in sheep or does it become some other nomenclature?

DR. DETWILER: I think only time will tell. I don't think we can predict that.

DR. BROWN: But, happily, there is no demonstrable infectivity in any dairy product in any TSE. So that is a good thing.

DR. DETWILER: That was the product--the broad distribution was the cheese.

DR. EWENSTEIN: I think,' to try to come to closure, on the Vermont flap, as you called it, I think that we can try to be reassuring in that the products that came out probably are very low risk products even though we don't fully understand the nature of the infection, itself.

So I think the part that I am struggling with, because I don't know enough about it, is the sort of deer-and-elk-meat exposure. Do we consider, at this point, that is sufficient enough if somebody has consumed large amounts or is in that industry to worry about them being potential--

DR. BROWN:, It wouldn't be the meat. It would be the velvet antlers because that is what would be in the supplements. Just substitute "velvet antlers" for "meat."

DR. EWENSTEIN: Okay, but are we--

DR. BROWN: We are just talking about dietary supplements. Therefore, deer and elk meat would not be at issue.

DR. EWENSTEIN: Why are we just talking about dietary supplements? Point 1 deals with all deer and elk issues.

DR. BROWN: I may be wrong.

DR. ASHER: Please address all exposures to chronic wasting disease, potential exposures.

DR. EWENSTEIN: Paul, point 3 was then focussing on the dietary supplements, but I think the issue had to do with the CDC's presentation on the young CJD exposures and whether there was any possible connection. I think that is the point that the committee should address one way or the other.

DR. BELAY: The BSE situation is different because we have enough ample evidence that BSE is actually a human pathogen whereas, in chronic wasting disease, we do not have any evidence that chronic wasting disease is a human pathogen.

It does not necessarily mean that there will never be a human pathogen, or it will never be transmitted to humans, but we do not have enough evidence to start formulating policies.

DR. BROWN: That brings us back to the original idea that we don't have any indication that blood is infectious either but we are deferring for six months. It gets back to the deferral, if you have stayed in Colorado for six months. If you follow logical consistency long enough, you get very illogical.

DR. LEITMAN: But we do have new variant. We know

that it has crossed the species barrier in the case of BSE. And we have no data to support that CWD will cross the species barrier. In fact, the little data we have from Cohee's study suggests that it is unlikely to do so. so I think it is a different group with respect to individuals who have been exposed to CWD and eaten elk meat and our level of concern at present.

DR. BROWN: I agree. And, incidently, we need, I think, unless the FDA stipulates that we have to, I think this part of the question--that is, so-called question 2, does not merit a vote. It merits discussion which is what is happening. Otherwise, we have to vote on every tissue, each disease, and I don't think we are capable of doing that.

DR. McCURDY: It seems to me that we have indicated that the Vermont sheep tissues and material that have been consumed are low risk. It seems to me that, with CWD, most of the meat is low risk. I think I would be unhappy at encouraging, or not discouraging, people from eating brain of brain products from CWD animals. I just don't know how to deal with antlers. I guess the antlers may be dealt with on the basis of the number of individuals that might be exposed and express some concern about that.

But I don't know--

DR. BROWN: And that is going to take an extended

trip to South Korea.

DR. McCURDY: No, thanks.

DR. DAVEY: Paul, I think we just want to make sure the committee has the direction we are going clearly in mind. I am concerned about what I have heard today. This is disturbing about the supplements, for sure. I took my glucosamine this morning.

I think to tie this all the way down to deferring blood donors is getting a little bit ahead of the game. What we need to be focussing on is regulating dietary supplements and the concerns we have about that instead of jumping ahead and saying we are going to have to consider deferring blood donors at this point.

That is a huge step and I think we ought to be very cautious before we make that--even a consideration of that. Our consideration, now, should be getting data about regulating these supplements.

DR. BROWN: I agree, but that was not, unfortunately, what we were asked to do. I have no input in terms of what we are being asked to do, but I think the gist of using blood donors., in a sense, was a mechanism to open up the entire issue to public discussion.

Therefore, we are not asked to do what most of us would really like to do which is to get the dietary-supplement people to get their act together and tell us

exactly what is going on. Rather, the window into that area is blood donors. I think that is the rationale.

DR. DAVEY: I am not sure that is the right window to be looking through right now.

DR. BROWN: But it is the only one we have.

DR. ASHER: It might be 'helpful if you attempted to keep the discussion of the various exposures separate. It would make it easier for us to intuit your opinions on them. There is no reason why a conclusion has to be drawn. I think that the agency now appreciates the level of concern and also appreciates the level of uncertainty. That might be sufficient for our needs.

DR. BROWN: **Do** you want us to consider each of the diseases now?

DR. ASHER: Yes.

DR. BROWN: Paul--was it Paul or Linda--there were two expressions that chronic wasting disease, per se, was--10; excuse me--the Vermont sheep issue, that anything having to do with Vermont sheep was extremely low--well, low risk and not to worry, no matter what the products. The products that were widespread were cheese.

DR. BOLTON: What about the animals, themselves?

DR. DETWILER: I'm sorry?

DR. BOLTON: Eventually, the animals will either die or be destroyed. Products derived from their eventual

demise, are we considering those as well?

DR. DETWILER: Oh; you mean the eventual demise?

DR. BOLTON: Yes.

DR. DETWILER: Oh; the eventual demise, they will either go up some chimney or through a sodium-hydroxide digester.

DR. EWENSTEIN: So if we are going to run through three questions, then the first one, which seems the easiest, is a decision that folks who have been exposed to these Vermont products do not have to be deferred. That seems to be the black-and-white question. That would be my opinion.

DR. BROWN: While we are at that, does anyone disagree with that? Are there any dissenting ideas? All right; we have disposed to Vermont sheep

DR. LURIE: I want to add something to Vermont sheep. I think that the scenario laid out by Linda is very worrisome. I think as long as we have been using this committee as a sort of the bully pulpit to make our concerns clear, I think it would be helpful to have the committee on record as fully supporting what the USDA has been trying to do in this area.

DR. FREAS: If I could add to that, our charge and mission, as this committee, is to make recommendations to FDA on FDA policies. We really are stepping outside of our

bounds of the mission of this committee. Advice is very good. Even good advice is very welcome to the right place.

I honestly think, in light of the mission and the large of this committee, for us to make recommendations ther than to the Commissioner of FDA, we are stepping out f our bounds.

DR. BROWN: The jury will disregard the last eclaration. We have dispensed with the Vermont sheep and ow we are on to--we haven't dispensed with the Vermont heep?

DR. BURKE: I am afraid we haven't. The rationale ight be this way. The Vermont sheep are the closest thing hat we have. If we were to make a hierarchy of all of the ther agents available to us, the Vermont sheep appear to be s close, perhaps, to BSE as another agent.

Thus far, we have said that the BSE agent is the one that we know has gone cross-species and, therefore, the one that would be most closely related to that, meaning sheep that might be infected with a BSE-like agent, would Logically be the next most worrisome thing.

I am not saying that that is sufficient grounds for deferral from donation, but just as a logical tree, that would make the most sense to me.

DR. BROWN: I think the point is well taken. I think the only thing that really tempers it is the products

that were distributed.

DR. ROOS: There were forty-five carcasses that were sold for human consumption but, as I heard, some of it went to the attorney.

DR. DETWILER: Just to put perspective, it was muscle meat that was sold and it was of lambs.

DR. BELAY: I would like, also, to bring to your attention that we are allowing people who have spent less than six months in the U.K. to continue to donate blood. So the question would be is the risk coming from people who have eaten the Vermont-sheep product a higher risk than what we have been allowing from the U.K.?

DR. McCURDY: Paul, I think, again, trying to put it in perspective, I wouldn't recommend anybody who had been eating brains from these sheep donate blood. I think they should worry, but my information is that nobody has eaten any brains.

DR. DETWILER: No brains.

DR. BROWN: That is what Linda said. It was strictly meat. Not only strictly meat, it was young meat.

DR. McCURDY: Strictly meat and cheese. Young meat and cheese. Those are low risk.

DR. BROWN: Right.

DR. EWENSTEIN: I understand, at best, these risk assessments are semi-quantitative. They are probably just

qualitative, but I think if you look at what Dr. Belay was saying, just taking everything together, the total amount of exposure to any one donor in the U.S., the kind of product that was consumed, et cetera, I think that this falls below, and if we are using six months in the U.K. as some threshold, and I know it is sort of an arbitrary threshold--but, if we are using that, this seems to be falling below that level, at least from what we know right now.

We have to make some sort of decision. Either we are going to start tracking these people down who had some of this cheese and say, you can't donate, or they can donate. I think we have, probably by consensus, agreed that they can. It seems like you can justify that on these sort of qualitative grounds.

DR. DETWILER: One other issue on the cheese, just because I know CDC, when they were requested for assistance here on milk and cheese, is that milk and cheese, by WHO or any milk and milk-products for known TSEs are not know to be associated with infectivity. So this would open this whole ball of wax on milk and cheese from Europe, actually, which does freely move in and is consumed.

DR. BROWN: Dispense with Vermont.

DR. BURKE: With logical consistency; thank you.

DR. BROWN: The next issue, then, is chronic wasting disease. I think everybody would agree that that is

in the middle of this triplet of hierarchies.

DR. WILLIAMS: I would just to say, and the committee has already said, that there is no scientific evidence that CWD is recognized as a human pathogen. Then, to make the jump, that, then, people will get it and then transmit it via blood, I think, going a little bit too far.

DR. BROWN: Is there a sentiment to put chronic wasting disease in the same low-risk category, then, as the Jermont sheep? Are they similarly unrisky? You are you think it probably is.

DR. McCURDY: Except for neural tissue.

DR. PRUSINER: I just think we know so little about chronic wasting disease that we don't know how to think about it. I think that is really what we ought to say.

DR. BROWN: Except we could probably say it is not a good idea to eat brain, I would imagine, from, say, an elk that died with chronic wasting disease.

DR. PRUSINER: I wouldn't disagree.

DR. WILLIAMS: And those are the recommendations that are given.

DR. BROWN: Right.

DR. BOLTON: Just to echo, I guess, what I said earlier, the fact that we voted that there is no evidence that it is a human pathogen does not mean that there is

evidence that it is not a human pathogen. So it is still an open question.

DR. EWENSTEIN: Excepting that, I think, we then still have to assign a risk. We have to, at least, determine that the risk is sufficiently high that we would want to defer donors. I don't think, speaking for myself, that we have crossed that threshold at this point.'

DR. BROWN: What it seems to me we are saying is that the risk in chronic wasting disease and the products there from, the risk in Vermont sheep and the products there from, both are likely to be small, but they are absolutely indeterminate on present knowledge whereas, the risk of BSE products is both demonstrable and finite.

Does that give the FDA enough guidance?

DR. ASHER: Yes.

DR. BROWN: Does anyone on the committee have any Further remarks to make?

DR. EWENSTEIN: The only thing is--well, I guess we have all said it before, but I would really urge the FDA to prioritize these products--and I know that they don't get to approve them ahead. of time so that they, then, have to prioritize what supplements to go after.

I don't suggest that they haven't already done this, but I would certainly think that the sense of this advisory committee is to prioritize those products that we

now have brain and neuronal tissue coming from cows of nknown origin as high on the list of those that should be nspected carefully.

DR. BROWN: Dave?

DR. ASHER: That answered it part of the way. It .s our take, then, that you are encouraging us to collect ore information because of the concern that the BSE agent ould be entering the United States in dietary supplements ontaining ruminant materials of unknown origin.

DR. BROWN: That comes to the end of a very packed wo days of meetings. I think I can speak for Ray and for tan. I certainly speak for myself that, after five years s chairman of the this committee, I want to thank every ember here present and past for their intelligence, their atience, their common sense and they have made my hairmanship a pleasure.

Thank you.

DR. FREAS: Thank you, Dr. Brown.

[Applause. 1

[Whereupon, at 4:25 p.m., the meeting was adjourned.]