be used to reduce the risk of sourcing materials from scrapie infected sheep. One which Lisa Ferguson will discuss later is sourcing from scrapie from scrapie free countries. The other is to source from scrapie free flocks in infected countries. The other is to test individual animals.

The problem that we have with this at this time is that currently the only validated test is on a dead animal, and many tissues are not acquired from dead animals.

There are two live animal tests under development by ARS. One is the third eyelid test, and the other is the capillary electrophoresis test. Neither test has been fully validated nor approved by USDA, and we anticipate it will be a while before that happens.

However, ARS has indicated to me, and I have seen literature from a commercial company, indicating that they intend to make the third eyelid test commercially available in the very near future, possibly even this month.

The other thing to consider is the genotype of the animals involved. Of course, by selecting for genetically resistant animals, you do not know whether or not based on current science

whether they contain the PrP agent.

For those of you who are not familiar with the third eyelid test, I threw this slide in just so you could see what it involves. It's a topical anesthetic on the eye, pulling back the third lid and snipping out a small portion of lymphoid tissue.

Okay. One option, as I mentioned is the source from free flocks within affected countries. USDA runs a voluntary scrapie flock certification program, which is based on the monitoring and self-reporting of flock owners. Possible additional criteria that could be added on top of requiring participation in this program would be to require the examination of tissues of all animals dying over 18 months of age. This is only currently required in the voluntary program for those flocks for which there is a suspicion that there might be scrapie, i.e., a trace or exposed flock.

The other option might be to require sentinel animals that are genetically susceptible to scrapie to be kept in the flock and to be examined upon death.

The other potential that's been suggested by some ARS researchers is to require that the entire flock be QQ in order to more rapidly detect the

presence of infection in the flock.

Once a live animal test is available, that, of course, would be a strong option, but we at this time do you feel that the live animal test that will soon be commercially available has been adequately validated, at least for USDA program purposes.

The other possible consideration is the past history of the flock with regard to scrapie, both of the animals themselves and of the premises on which they're being reared.

The other consideration is whether or not the flock should be required to remain totally closed as opposed to allowing the movement of animals as is currently permitted in the program.

And the other option is to consider the feeding practices for those animals, which is not a requirement currently of the program.

Now, I'm going to discuss some of the specific details of the voluntary program as it currently exists. These are the numbers of participating flocks. As you can see, we've got a large number throughout various areas of the U.S. We currently have 27 scrapie certified free flocks.

There are two potential categories in

which a person can enroll in the voluntary program. One is the complete monitored category, and that's the only category that allows a flock to progress to certified free status.

The other category, the selective monitor category, is primarily intended for commercial producers who produce slaughter lambs. The intent is to provide them with a way of monitoring for scrapie based on examination of cull ewes prior to slaughter and with any animals that look clinically suspicious being sent in for diagnostic testing.

The general provisions of the voluntary program are that the owner agrees to report any scrapie suspects. They agree that should a suspect be found, to allow that animal to be euthanized and those tissues collected and submitted for diagnosis.

They also agree to identify all animals over a year of age with a relatively permanent form of ID, such as a tatoo and electronic implant or a tamper resistant ear tag.

They also must identify any animal being sold for other than slaughter purposes no matter what its age.

They are required to keep records, and those records are inspected on a yearly basis, which

includes all identification that's found on the animal, the sex, age, and breed of the animal, the date of birth or the date of acquisition and which flock it originated from, sire and dam identification information, progeny identification and sex, and the disposition of that animal, and should it have died, the presumed cause of death.

They are also required to provide us with authorization to contact any breed association with which they might have registered animals should it become necessary to trace out any animals from the flock.

They also are required to notify us within 30 days of any acquisitions that are not in compliance with the program or that would lower their status.

Each of these flocks is inspected by a federal veterinarian or a state veterinarian every 11 to 13 months. The main thing that is done at those inspections is to review the identification on all of the animals, and then to check that identification against the inventory records and determine the disposition and acquisition of all animals.

Also, the animals are observed for any potential signs of scrapie, and any animals that are suspicious are identified and rechecked as needed, and

if it becomes clear that they are highly suspicious, then those animals are euthanized, and the tissues are submitted for diagnosis.

There are two potential statuses within the complete monitored program. One is enrolled, which simply means that the producer is participating, and the other is certify which means that they have been continuously in compliance with all of the standards for a period of five years.

Female animal acquisitions and commingling requirements. In other words, how can a person get a female animal from another flock? Basically a certified flock can only acquire a female animal from another certified flock. Enrolled flocks may acquire female animals from any other enrolled flock which has a similar or older status date than they do, in other words, have the same risk level or less.

The male animal acquisition requirements are less stringent for two reasons. One is because we believe the male animal to be at very low risk of transmitting scrapie, and the other is that sheep owners need to bring in new genetics into their flocks or they can't have a productive and viable flock.

In order to acquire a male animal, the animal must be officially identified, must be shown on

the flock inventory, and he must not have been exposed to scrapie, cannot be a scrapie positive animal. He can't be a scrapie affected animal, can't be a scrapie suspect, can't be exhibiting any clinical signs, have been designated high risk or have originated from a source or infected trace or exposed flock if his actual status can't be determined. Also, he cannot currently reside in an infected or source flock.

For certified flocks, there's also been a small tightening in the new version, which is the yellow book that you've all received in which it states that a male animal must be acquired from an enrolled flock, and that animal must have resided in that flock for at least a year or have been borne there. Previously that was not a requirement.

Likewise, for female animals in certified flocks, they can only commingle with female animals from other certified flocks, and they may not reside in the kidding or lambing facilities of anything other than another certified flock or their own flock.

We did have a problem with that, and that's why we've made that change.

Commingling of male animals. It is permissible under the current program for rams from certified flocks to be permitted to be leased to

nonparticipating flocks for the purpose of breeding, but they may not be exposed to female animals at or near lambing or for 60 days after lambing. They may not be housed in lambing facilities, and they may not reside in any other flock except the certified flock, except for the purpose of breeding.

And if they are used in a flock that is known to be infected, source traced, or exposed, then they cannot return to the certified flock without them losing their certified status.

Should there be an occurrence of scrapie in a certified or enrolled flock, that flock is removed from the program.

Other actions that can potentially affect the status or status date of an enrolled flock is the use of semen and embryos. For semen, basically the standard is the same for the acquisition of male animals. They may use semen from any flock unless that animal is himself scrapie positive or unless that animal is a high risk animal or is of unknown, undeterminable status based on his previously having been in an infected or source flock.

For embryos, the standards are basically equivalent for those for female animals in that the embryo must have the same status as the flock. In the

case of certified flocks, the embryo would have to come from a certified donor.

For imported animals, basically the animal would either have to come from a scrapie free country or the animal would have to have been participating in a program equivalent or more stringent than the American program as evaluated by USDA and be an equivalent level in the program in order to be imported into a participating flock.

That's all I have. Any questions?

CHAIRMAN BROWN: Thank you.

We will entertain questions for Dr. Sutton, as for the next two speakers, without waiting until the end.

Stan.

DR. PRUSINER: I'm curious about your ideas about the genotyping of these sheep and if you use, for instance, an RR 171 sheep, and you think then that the scrapie agent, freon, whatever, virus goes underground.

CHAIRMAN BROWN: "Whatever" is the preferred term here. Okay?

DR. PRUSINER: Right. We got that one yesterday, right?

(Laughter.)

DR. PRUSINER: That goes underground and you can't find it then. That's what you said, I think.

DR. SUTTON: What I said was the research is insufficient at this time for us to know whether the scrapie agent is present in those sheep or not.

DR. PRUSINER: Okay. I don't know how to proceed here. Let me just take two -- I'll make this very, very brief.

I mean, I think that you really ought to consider an alternate view of all of this. These animals that these basic residues like arginines create dominant negatives in these animals. The same thing is true in humans, and I think that's a very plausible explanation.

It's not proven, but it looks very good now, and it's not acknowledged at all in this book. so it's for the record.

I'll stop.

DR. SUTTON: One of the primary reasons that USDA has not yet accepted genotyping as a means of scrapie control for official purposes is because there is one case report in the literature of an RR being clinically affected with scrapie, and there are four case reports of QRs being clinically affected

with scrapie, and our experience -- I probably shouldn't mention this -- with the New Jersey pilot slaughter project suggests, although that information is unpublished and not complete yet, that the genotype may not prevent PrP scrapie RES from being found on immunohistochemistry.

All of these make us suspicious that there may be an infectious agent in these animals.

DR. DETWILER: Can I further comment on that since that's what I think Jeff Almond was referring to about this little pilot study? But all of the questions that it brings up is that we have found the different genotypes with PrP-RES, but again, if they were positive across the board in these, then it would make you feel better.

And there were animals that were clinically asymptomatic, that were positive in the brain, in the lymphoreticular tissues, but then you had ones mostly in these other genotypes where you might have the tonsil or lymph node or the brain. Then you had an IHC positive, but not the Western blot, but we can even wonder about those that its collection techniques -- that you don't test the same part of that tissue with the different methods, you know. So it's not the exact same thing you're

testing.

But they just leave us with more questions than they do really answers.

CHAIRMAN BROWN: Stan?

DR. PRUSINER: Yes, I think you want to make -- did you want to talk first? Go ahead.

I just wanted to say that I don't think that the protease resistance of PrP is an absolute indicator of infectivity. It's a surrogate market, and when it's there, it's useful. When it's not there, it becomes problematic.

So you can't use this as an absolute. I mean, we have multiple transgenic models now, and we have some human diseases like GSS 102 where proteinase K resistance is really not a good marker. So you have to be careful of this.

That's why we developed this new assay where we're looking at a buried epitope and then a form of PrP that has a high beta sheep content.

So I think you have to be very, very careful of how you interpret this.

DR. DETWILER: That's why we haven't published those, but do you want to test some tissues for us?

(Laughter.)

DR. ALMOND: I'm not quite sure where we're going in this other than to say it is difficult to interpret. The studies of Nora Hunter suggest that different or certain genotypes of sheep are much less susceptible to certain strains of scrapie, but if you change the strain of scrapie, the pattern becomes rather different.

One of the most interesting observations that she's made in recent years is that certain genotype -- and I can't remember if it's 136 or 171 -- but in the U.K. environment, those sheep inevitably, almost inevitably develop scrapie, and yet she's found that same genotype in New Zealand, and they're completely scrapie free, of course.

And then there are other observations as well that relate to this. Moira Bruce, for example, with Richard Kimberlin did some transitions of CJD to mice. The mice didn't develop any illness in their lifetime, but when they were examined in old age, they had some spongiform change in their brain, suggesting that they were, in fact, incubating a spongiform encephalopathy, and the implication of that could be that this was a disease which was taking more than the life span of the animal to actually develop itself as a clinical disease, but potentially there could be a

source of infection to other animals with adaptive passage that, therefore, actually represent the reservoir.

And I did raise the question in my presentation about whether there is silent infection. So there could be a reservoir of prions which you simply don't see because in that particular genotype of animal the incubation time is longer than the life span of that animal.

CHAIRMAN BROWN: Kiki?

DR. HELLMAN: I just have a question. Kiki Hellman, FDA.

I know very little about sheep, but I would imagine that somewhere there must be a lineage history of the different breeds of sheep that we have today, where they derive from, where they're found. That might help us.

And now, of course, since you are introducing different breeds, you get hybrids and so on, but that might help us in perhaps the evolution of scrapie or the agent. It's just a thought.

DR. SUTTON: Actually a part of the presentation that Nora Wineland lent to me did actually address that and showed where the various breeds came from, and I don't think one could make an

argument that it was directly due to these animals being mixed and that follow along breed lines.

I think it's pretty well accepted that it was due to lateral transmission.

CHAIRMAN BROWN: Dean?

DR. CLIVER: Yes, as another non-sheep person, it would be helpful in some of these summaries that you presented had you used prevalence data rather than incidence data. Like we saw an enormous number of Suffolk that had succumbed, but we have no idea of what rate that represents against the population of Suffolk in the United States.

DR. SUTTON: Right.

DR. CLIVER: So that annual prevalence, state prevalence, things like that, we who don't look at these figures very often get a better sense of what's going on if they're presented as prevalence rather than --

DR. SUTTON: The breed data that I showed was for the entire 1,503 sheep for which we had data from the history of, for instance, the start of scrapie in the U.S.

Suffolk sheep are the largest pure bred sheep that we have as a breed, that we have in the U.S. currently. What number they represent out of

that entire group, what the relative percent is, I'm not absolutely sure.

DR. CLIVER: Well, I wasn't expecting you to be able to deliver that from the hip, so to speak, but just as you're compiling data for this kind of a group, it's really helpful to give it on a prevalence basis.

DR. ROHWER: You very nicely have described the scrapie control program, but didn't say anything about how effective it was, and I see a big disincentive in this program to reporting scrapie if it should appear in one of these flocks that people have expended a great deal of money and effort to establish, and then what if they do get -- in introducing new stock, they do introduce scrapie into a flock like this? Can they really afford to report that? I mean with a decade or more of hard work to establish what they've got already.

And do you have any experience yet -- I mean, is the program established enough to know how successful it has been? Have people had problems like this, or how is it working?

Also, what percentage of the sheep industry has enrolled in this program?

DR. SUTTON: Okay. The program stated in

1992. We currently have 419 enrolled producers, which is a dramatic increase over last year. We've had a 75 percent increase.

Of those, 27 have reached certified status, which means they've been enrolled for at least five years, and that would make them compliant with the program for that duration of time.

Of the flocks that have reached certified status, we haven't had one go down with scrapie yet, which doesn't mean it won't potentially happen.

We have had flocks that were at the lower levels of the program that had infection discovered and were moved back, either taken totally out of the program or went out of the program and then reapplied.

CHAIRMAN BROWN: What proportion of sheep -- I may have missed it, for which I excuse myself -- what proportion of sheep in this country are enrolled in the program?

DR. SUTTON: Okay. We have 7.2 million sheep in this country and approximately 68,800 flocks. Of those, approximately 17,000 are what are called seed stock producers. Nearly all of the enrolled producers are seed stock producers. So we have approximately just under two percent of our seed stock producers enrolled at this time.

CHAIRMAN BROWN: Seed stock being breeders?

DR. SUTTON: Correct.

CHAIRMAN BROWN: Two percent of the breeding population or the flocks used primarily or exclusively as breeders are enrolled in the program.

DR. SUTTON: Correct.

CHAIRMAN BROWN: Okay. Ermias.

DR. BELAY: I just wanted to clarify one issue. The ban on importation of live animals from countries where BSE has been identified that the USDA put in place in 1989, does it include sheep and goat in addition to cattle?

DR. SUTTON: Yes.

CHAIRMAN BROWN: Ray?

DR. ROOS: I guess there was some brief discussion about susceptibility of different breeds, and I guess what I heard is that one polymorphism was discussed as far as in the PrP and how effective it was as far as determining susceptibility.

Now, am I correct in thinking that there must be a lot of other genetic determinants outside that PrP, polymorphism, in other words? Some breeds that have identical sequence of PrP nevertheless have very variable susceptibility or isn't that known?

DR. SUTTON: You're out of my area of expertise, but there are at least three codon areas on the PrP that are related to susceptibility, 136, 154, and 171.

DR. DETWILER: I can add a little bit more on that. It does depend what breed. There are some breeds that are called the 136 breeds, and the other breeds they call the 171 breeds. The Suffolks are 171, where that's the main dependency.

And it does seem like most breeds follow that 171 with the arginine homozygotes of being only one reported case of clinical scrapie, and then you have breeds like in Britain that would not follow the U.S. pattern. They're the 136 breeds that valine homozygotes are what they call their positive line and alanine homozygotes, but in the U.S. almost all of our sheep are alanine at 136. So that does not in this country appear to play a role.

DR. ROOS: But is there anything outside the PrP gene polymorphisms that look important?

DR. DETWILER: Not to my knowledge, but I don't know.

DR. ALMOND: Actually there is in mice. Stan will help me with which is which, but you know, the S7P7, as they used to be called by the Edinburgh

Group; I think it's VMs and 357 blacks that are both P, and they have different incubation times, and if you do crosses between those, you get intermediate incubation times.

I am aware that there are experiments in progress which are trying to map the determinants of the differences in incubation time in mice strains where the PrP gene sequence is identical.

DR. PRUSINER: I think these differences are very small though, Jeff. I don't think they're large.

DR. ALMOND: Well, the issue -- well, I know they're small. They're still measurable actually in 100 days type level or 80 days. The point is they're entirely reproducible, and when you make the hybrids, you get something in between.

When you do R3 mice or VM mice, you have a tight cluster around the endpoint, and when you do C57.blacks you have a distinguishable, but again a tight cluster. They are reproducible. They are not related to PrP gene sequence because that is identical in the animals.

CHAIRMAN BROWN: Would it be a fair summary of this entire discussion to say that the genotyping of sheep unfortunately turns out not to be

a straightforward, simple matter, and that it is in flux, and that eventually it may get shaken out, and one will find one or more really crucial points on this or another gene which will clarify matters?

But at the moment, sheep genotyping and its relationship to susceptibility is in evolution.

DR. ALMOND: I think one would also add that unlike the situation in cattle, and of course, we've looked at a lot of cattle of different breeds in the U.K., the number of polymorphisms in cattle is very small. You have the five versus six off the peptide repeat, and that's about it.

Whereas, of course, in the sheep there are all sorts of polymorphisms scattered across the different breeds, and it's much more difficult then to interpret scrapie susceptibility.

It may be saying something about the co-evolution of TSE in sheep, and therefore, there's been selection pressures on certain prion genotypes in sheep which hasn't existed in cattle. I don't know, but it is more complicated in sheep.

CHAIRMAN BROWN: Bob, yours is the last comment.

DR. ROHWER: Oh, if I only get one comment, then I'll get off genetics. I want to go

back to the question that Dr. Belay asked and make sure that we're absolutely sure on this.

It seemed to me that you left open a loophole at the end of your presentation there for importation of animals from BSE affected countries if they met certain standards or something like that, and I'd like it made perfectly clear whether that can happen and whether that provision, if there is a provision, extends to the wider provision that was implemented and that was laid down in 1997 for BSE to all of Europe, et cetera.

DR. SUTTON: For imported animals, that restriction applies. These would be imported animals from countries that are not known to be affected with BSE and are not believed to be at risk of BSE, that are not currently excluded, or at least it can better answer that.

DR. ROHWER: I'm not sure what distinction you're making.

DR. FERGUSON: Okay. Let me clarify a bit. Our initial import restrictions that we started in 1989, we applied to countries that had diagnosed and identified BSE in native animals, and those restrictions were for all ruminants. It was not just cattle. It was for all ruminants, including sheep,

goats, cervidae, llamas, whatever. Ruminants from BSE affected countries were not allowed in.

Those same restrictions, the end of '97, January of '98, publication of the interim rule, when we extended those restrictions across all of Europe, again, those same restrictions applied. It was all ruminants that could not come in.

Now, the comment that Dr. Sutton made in her program about allowing imported animals into the voluntary program, that would come from countries that were not restricted due to BSE, and a big chunk here would be let's take Canada as an example. So, you know, those types of animals could come from that type of a country, and they could go into a flock enrolled in the program only if they came from a flock in that other country enrolled in a similar or equivalent type program.

Now, there could be imports going into nonenrolled flocks. That would not be coming from flocks in that other country in a similar type program.

Does that help or have I confused things even further?

DR. ROHWER: I think that helps, but maybe a better example would be Mexico.

DR. FERGUSON: Mexico is a touchy subject, and I was going to get into a little bit of this in my talk. So now hopefully I can leave it out.

CHAIRMAN BROWN: I'd prefer you left it in and stop now.

DR. FERGUSON: Okay, okay.

CHAIRMAN BROWN: As long as it is going to be included.

DR. FERGUSON: It will.

CHAIRMAN BROWN: So thank you very much, Diane.

Our next speaker is Dr. John Honstead, who reminded me that I was remiss in not introducing this Committee to a very distinguished gentleman. I use that word in its literal sense, who for at least three decades was Mr. Scrapie for the USDA, and that's Dr. Jim Hourrigan.

Would you stand up, Jim, and let people see who scrapie was all about?

(Applause.)

CHAIRMAN BROWN: Jim has heard these same questions about 50 times, and the same answers keep coming back. It's very difficult to get precise, happy, satisfactory answers to virtually every question we ask on the topic.

John.

DR. HONSTEAD: Thank you very much, Paul, and thanks, Jim. I don't know if you ever thought your work would be used by FDA, but it is, and it's still today very useful, and Jim comes to a lot of animal health meetings, and it's great to have him around.

I'm John Honstead. I'm from FDA. I'm a veterinarian with the Division of Animal Feeds, and that's the reason we're involved in BSE.

I'm going to give you today the briefest summary of the FDA regulation that's ever been given in history. Because it's going to be so brief, I think it's really important that you have our Web site: www.fda.gov/cvm. It's very simple.

On that Web site are a lot of support documents for the regulation that we've prepared for industry and for anybody to help explain this and make it understandable and get it fully implemented.

Okay. Epidemic curve for the British epidemic and slighted a little bit to the -- I just want to point the other way. I just want to point out here that the rate of decline in Britain has slowed down dramatically. They had originally predicted a decline to insignificant levels in Britain by 2001.

This is the British government, and their last report no longer says that. It says that the rate of decline is very slow, and we don't know when it's going to end.

So they may have an endemic situation there for quite a while. We don't know.

Next.

The FDA BSE feed regulation went into -- was finalized in June of 1997. It is a mammalian to ruminant ban. Mammalian proteins are prohibited from being fed to ruminants in the United States.

It is a protein ban. It only applies to proteins. It does not apply to fats. It does not apply to mineral supplements where there is no protein in them. It's only mammalian proteins. It does not apply to fish products, fish meal or poultry, feather meal and such from non-mammals.

And there are five exemptions to this regulation. It does not apply to pure swine and pure equine proteins where these come from a renderer who only does pigs and horses. Now, there is no such renderer for horses, but there are several renderers that do nothing but pigs, and so this protein is acceptable for ruminant feed.

Blood, milk, and gelatin and those types

of products are exempt, and plate waste, which is food that's been prepared and cooked for human consumption does not get used or it's not eaten that day, and it is reprocessed for usually cattle feed. This material has a very small amount of meat in it. All of the beef in it comes from USDA inspected, healthy, non-CNS animals, and it's reheated in some sort of process for cattle feed, diluted with large amounts of corn to balance the ration.

In general, the regulation requires -- I have to say that in the past before this regulation, everything was rendered together in one big process. There was never any reason to suspect that anything in any of the proteins in meat and bone meal was of danger to any animal, and so in 1997, this sounds like a simple change, but this in effect was a humongous change for the feed and cattle industry to accomplish. It's very difficult.

Renderers and feed mills must separate the prohibited materials from non-prohibited materials if they handle both, and they must have a written plan to describe and follow as to how they'll do this.

They must label everything that has prohibited proteins in it with the statement "do not feed to cattle or other ruminants." They must keep

records sufficient to track the incoming materials and their outgoing materials. They must keep these records for one year, and these records have to be made available to FDA or state inspectors upon request in an investigation.

For renderers, and these are the people that take the fresh gunk and cook it into water, fats, oils, and the bottom stuff in the pot is protein, and it makes an excellent animal feed.

If they handle both, they can choose to separate or not separate prohibited and nonprohibited materials. If they separate it, again, they have to have a plan. They must clean their equipment between the two, and they must follow this plan.

Most renderers are not separating it. It's not efficient for them, and they simply specialize. They either handle prohibited or they handle nonprohibited.

They must, again, label it, and this labeling for renderers which generate very large amounts of this protein is usually in the form of statements on the bill of lading, the shipping materials and those sorts of things, as well as placards, possibly on the rail cars themselves, and it would say "do not feed to cattle or other ruminants."

Their records would have to be able to trace the incoming materials and the outgoing materials, and they would have to keep these records for one year.

Protein blenders, in between the renderers in this country and the people on the farms feeding cattle is a huge system of brokers, feed mills, protein blenders, distributors. Some people only handle this stuff over the phone. Others have trucks and haul it, and it's very complex.

Those people involved in that also have the option of separating or not separating it, and many feed mills have simply gone to absolutely no prohibited material in their operation if they're making feeds for a variety of animals including ruminants.

They have to label any feed products containing prohibited material with a statement "do not feel to cattle or other ruminants," and this label has to be prominent. If it's a bag of feed and these bags are printed, then it has to be on the bag itself. Many bags just have a feed tag on it. It must be very prominent on that sewn in feed tag.

Again, they have to keep records to track it, both incoming and outgoing, and keep those records

for one year.

People that feel ruminants, and this falls into two large categories, producers that mix feed on their farm and producers that buy a complete feed and don't do any mixing at all.

Again, they have to maintain all incoming feed invoices so that they can have proof or identification of whether they're getting prohibited materials. They have to keep these labels, and certainly they have to obey the label, and the paper work has to be made available to FDA and the state feed inspectors on request. They have to keep these for one year.

Pet food, you won't find this statement on pet food in the grocery store. Retail pet food going to grocery stores is generally not fed to ruminants at all. It goes to cats, and it's in grocery stores, but as soon as pet food is damaged or unacceptable for use in pets and it gets diverted away from the retail pet food market, it then falls under the regulation and must be labeled.

Now all of the other paper work, tracking, and records is maintained for pet food. They do have to keep records. They simply do not have to label the retail package.

In conclusion, the long incubation period that we've heard a lot about the last two days, it could lead to undetected amplification of BSE in the United States if we recycled ruminant mammalian proteins back to ruminants. So its intent is to prevent undetected amplification of BSE in U.S. ruminants.

It identifies prohibited materials with the label, and it bans the feeding of these prohibited materials to ruminants.

There's a tremendous amount of cooperation going on in the United States. Two-thirds of the inspections have been done by state feed inspectors and the data and the results from those have all been sent to our Center for Veterinary Medicine, and this has been a great cooperative effort, and as we've always heard, we need more research in BSE so that we could understand the implications of U.K. BSE and BSE in sheep and all of these things to this country.

So sheep materials and cattle materials cannot be recycled back to cattle and sheep in this country through animal feeds.

Thank you very much.

(Applause.)

CHAIRMAN BROWN: Thank you, John.

We have time for one or two questions. Stan?

DR. PRUSINER: How did you decide on the one year record keeping?

DR. HONSTEAD: That is a requirement so that we can find out as we show up at an operation as to whether they're in compliance with a regulation. It is not intended to help us or USDA trace a case of BSE's feeding history.

There's a Paper Work Reduction Act now in effect for the entire federal government, and it makes it difficult to impose large amounts of paper work to our customers. One year would suffice for us to see if you're doing -- if the farm is doing its job right. We would have to look at whatever paper work was available in case we were trying to follow up on the feeding history of a case of BSE.

DR. PRUSINER: Okay.

CHAIRMAN BROWN: Bob.

DR. ROHWER: John, we're all very pleased with the implementation of the feed ban, but of course, it's only as good as it's being followed, and how are you going about ascertaining the level of compliance and assuring yourself that it is actually being implemented fully?

DR. HONSTEAD: Of course, it's not 100 percent implemented. We would love to see that, but it's such a huge change and many, many, many of the animal producers are very small, and what we're doing, every inspection performed fills out a two page set of data, questionnaire. That is sent to CVM. We put it in a database, and from that we have an understanding, but non-random, of course.

These BSE inspections are generally performed in conjunction with some other reason to visit the feed mill or farm, and so we have collected this data, and the compliance rates are different for renderers, feed mills, and producers, but they're very encouraging. Almost all of the renderers are doing their job right.

And when the rendering material, meat and bone meal is done correct, then it, of course, gives you a chance for maintaining the feed ban throughout the industry, but we have not done randomized sampling. Our inspections are not random. So we don't have nationwide statistical information on compliance.

CHAIRMAN BROWN: Yes, last comment, Jeff. Oh, sorry. After Jeff, Dave, and then we'll move on.

DR. ALMOND: Okay. Just three very quick

comments. The first is I was a little surprised that your plate waste recommendation meant that that material could still be used, the point being there will still be sheep material in that plate waste, and it will include catering waste where you may have essentially the whole of the spinal column of a sheep going back into the rendering industry.

If sheep is the source of VSE, then that would allow the possibility of the spark of BSE cases here as it may have done in the U.K.

The other thing, of course, is the amplification and just elaboration on that. The back calculation method of Anderson and colleagues suggest that at the time when Gerald Wells made the diagnosis of the first two cases of BSE in the U.K. in December 1986, that by then we had 60,000 infected animals. So this disease with that incubation time in cattle of five years, you know, really does amplify before you see it.

The final comment I wanted to make was on your indication that the BSE epidemic in the U.K. is not declining. I accept that the latest figures do show a tailing, and it's not absolutely clear why that is, but in the mathematical modeling of Anderson, a tail is expected depending on the relative

contribution of the final animals being derived from either maternal transmission or leak, leakiness in the feed ban.

Now, the feed ban no longer leaks because we banned meat and bone meal for any animal products. They should never go near the farms as of April 1996. So what's left, new cases should be only maternal, and we were prepared for a tail if a majority of those cases we're seeing now are indeed maternal.

The point about it though, as Anderson points out, you would not get -- we are pretty confident or very confident that you will not get endemic BSE in cattle because the R zero value is clearly below one. The R zero value is the number of cases from any one case of BSE that you observe, and the transmission has to be one in order for it not to die out.

So even if there is some transmission cow to calf and some transmission animal to animal, it will disappear because the R zero value -- the epidemic we've observed is not -- is not compatible with an R zero value above something like .1. So it really will go away. It may have a long tail, but it will go away. That's our position at the moment.

DR. HONSTEAD: Thank you. I appreciate

that.

I said that the rate of decline was decreasing, but I didn't say there was no decline. There is a decline. It's just slow. Thank you. Thank you for that.

CHAIRMAN BROWN: Do you want to respond to the plate waste and then we'll go on?

DR. HONSTEAD: This reg is written for country right now without BSE, and the plate waste is, again, from animals with no CNS diseases, and it's a very small amount, and even though heating won't completely, of course, inactivate this, it is our requirements for reheating for animal feed are associated with pelleting machines, which do get it hot, and it just -- this would present, you know, a very, very small risk in a BSE-free country.

And I agree with what you say about what they felt like in England when they found their first cases, but the longer this ban's in effect and the longer we are BSE negative, then it's pretty difficult to think that this poses a significant risk.

CHAIRMAN BROWN: Dave.

DR. BOLTON: Yes. A question regarding -- a two-part question regarding compliance. Do you have any idea what the cost differential is to the end user

of the two types of feed now?

And the second part is: what are the penalties for the end user of being in violation of the use?

DR. HONSTEAD: The cost differential, you mean for something like pure pork protein versus mixed prohibited materials?

DR. BOLTON: Right.

DR. HONSTEAD: I don't have those with me. You can look in the Feedstuffs magazine, and they may have something on line, but they track the prices of this stuff, and it changes a little bit, but it has not been a type of cost that would break an industry or put anybody out of business.

It was much smaller than the renderers predicted it would be.

DR. BOLTON: It's not sufficient then to induce somebody to risk any penalties that they would incur by using that feed as opposed to using the correct feed?

DR. HONSTEAD: I don't think so because there's been a lot of specialization. The hog plants are putting out a very good protein. There are also uses for all prohibited materials. It can be used for hog feed, horse feed, and one of the biggest uses of

all these proteins is pet food, and so our reg did not interfere with a great deal of use of these proteins. It just caused them to be separated and identified, and the larger renderers, which is what most rendered product comes from, only a few very large renders; they specialized, and so these markets are being utilized to accomplish the goals of this economically.

And there was a change, but it has not been dramatic, and it is working very well right now.

DR. DETWILER: John, can I just add that -- it might help answer Dave's question, too -- no, usually the differential is not enough to cause somebody. That would be economic incentive.

The other thing, the availability of the soybean protein here in this country, too, gives another big area of a protein source.

CHAIRMAN BROWN: Thank you very much, John.

We now have our last presentation before lunch from Dr. Lisa Ferguson, Animal and Plant Health Inspection Service of the USDA.

Dr. Ferguson.

DR. FERGUSON: And bear with me for a moment here while I get the computer up and going again. It worked for Diane. So we're hoping it still

works for me.

(Pause in proceedings.)

DR. DURFOR: Mr. Chairman, could I take this opportunity to ask a question of Dr. Almond?

I would find this R value calculation much more persuasive if the same analysis had been applied to scrapie because I wonder if you'll get an R value of greater than one for scrapie because of the way in which the endonicity manifests itself at very low in herd incidences and very long incubation times.

DR. ALMOND: I haven't done those calculations, the work of Roy Anderson and his colleagues. So I couldn't precisely tell you whether the comparison with scrapie has been made, but what you do have in BSE is a very, very strong evidence of a falling incidence, and if there are no -- above one, you would not have a falling incidence, and since the beginning of 1993, we have fallen from 4.3 thousand cases a month down to 300 cases a month.

So I think there is plenty of evidence there for a negative R value or a less than one R value in the cattle, and I appreciate that we probably don't know what it is in the sheep.

DR. ROHWER: I mean, I understand that. I'm very familiar with the epidemic curve, but I just

wonder if the same thing wouldn't be true for sheep. For example, after the vaccine, the loping L vaccine incident, there was apparently a bolus of scrapie which then subsided again back into endemic levels after that incident, and how do we know that this isn't going to happen with BSE as well?

I understand the calculation. What I'm saying is I think in nature we have an opportunity to test the validity of that observation by looking at scrapie itself and seeing how well that number plays out.

DR. ALMOND: I accept, and I'm the wrong person to be answering your question, other than to say Roy has looked at this quite carefully and has concluded that the R value for BSE in cattle really cannot be anything like approaching one, but I do take your point that when you have an epidemic spread around by something else, the decline because of then the removal of that something else may take you back down to a low level which is enough to establish an endemic disease, but I think we just have to wait and see.

CHAIRMAN BROWN: Dr. Ferguson is now ready.

DR. FERGUSON: Thank you for bearing with

me. Sometimes I think these machines are smarter than I am. That doesn't make me feel very good.

Anyway, I'm sort of, I guess, the clean-up hitter here this morning, almost this afternoon, and I think my colleagues have covered a lot of good points. I'm just going to cover a few new ones and then recover or rehit some high points especially that were in Dr. Sutton's presentation.

What is on the agenda was for me to talk about measures for consideration in assuring scrapie free sources of sheep and goat derived materials, especially from countries where scrapie is present. However, I thought I would take this opportunity to also share some information on surveillance in those countries where scrapie is absent. I thought that might be useful, and then, as has been identified also earlier, kind of how we at USDA look at other countries, especially in regards to scrapie and the import of sheep and sheep genetics.

So let's start off. Scrapie free sources, boiled down very simply, you kind of have two options with some other considerations. The two options are a free country and/or a free region, a free zone. You can define your geographic area, or you can have free flocks.

So let's start off scrapie free countries. Traditionally, we at USDA have recognized Australia and New Zealand as free of scrapie, actually free of other TSEs also, but for purposes of this presentation, I'm going to focus on scrapie.

Other countries have requested recognition. Specifically, South Africa has sent us quite a bit of information. This is currently under review. We haven't reached a final conclusion yet. So I can just kind of give the high points of what they have submitted.

There probably will be others in the future. Mexico has already been brought up. That is one that has requested it. We haven't gotten very far with that, but I'll go into that in a bit more detail.

So let's start off with our colleagues down under. What are they doing and how have we assured ourselves that they are free of scrapie?

First of all, Australia. To start with, they have a very strong veterinary infrastructure. We have faith in the fact that they do have solid veterinary services both from a federal and a state standpoint, and that they have adequate resources at a diagnostic level and also as a regulatory authority to diagnose scrapie and to control it if it did show

up.

They have very stringent import controls not only just for scrapie, but for all other diseases. Since they're an island continent, they've been able to maintain a very high animal health status by virtue of their stringent controls.

They have identified scrapie, and 1952 was the only occurrence. This was in Suffolks that had been imported from the U.K. I believe they were imported in 1950, and they diagnosed the disease in 1952. The animals were still under quarantine. They were not on an offshore quarantine. They were in Victoria, but they were still under APHIS' control.

They slaughtered all of the affected and in contact animals and have not really had a problem since.

Scrapie is a notifiable disease. All nervous system disorders are investigated, brains examined. They are doing surveillance. Since 1990 they have looked at greater than 2,400 brains. I don't have an exact figure, but that at least will give you an idea.

And how does that relate to their population? Australia has a lot of sheep, 120 million sheep, but one significant fact. A vast majority of

those are the Merino breed. That's a wool breed, not really high prevalence for scrapie.

Okay. Let's move over there across the Tasman Sea and talk about New Zealand. Again, New Zealand also has a very strong veterinary infrastructure. They also have stringent import controls.

They, however, have had two incidents of scrapie. Similar the first time as in Australia, 1952 and 1954. Again, these were Suffolks that were imported from the U.K. They initially had identified scrapie in 1952 and slaughtered those affected animals. However, in 1954, there were some contact herds, and some of those initial imports had moved around. So they diagnosed the disease again in 1954.

And they slaughtered all of those affected herds and contacts and did not have problems again until in the 1970s. They decided they would again some imports from the U.K., and these animals were still in the offshore quarantine.

Both Australia and New Zealand traditionally are using the offshore quarantines for their live animal imports.

And these were different breeds. In 1976, the first one was an East Friesian sheep, and in 1977

then it was a Finnish Landrace. These both were from the U.K., but different breeds.

All of those imports then were slaughtered and were never released off the quarantine.

Again, scrapie is notifiable in New Zealand. All nervous system disorders are officially investigated. They also are doing fairly active surveillance, greater than 1,100 brains sine 1990, and this figure here, greater than 325 since 1994, that just breaks it down a bit more for you.

How many sheep do they have? They also have quite a few, 50 million sheep, but they have various breeds. It's not the high preponderance of the Merinos as in Australia.

Countries under review. South Africa has requested that we recognize their status in relation to scrapie, and our review has been ongoing for a while. They have diagnosed scrapie, in 1966, and they did a very stringent eradication program and eradicated the disease in 1972.

Sine that time, they've had an active -- well, an ongoing both active and passive surveillance program. They have looked at many, many sheep brains. So initially our review is fairly favorable.

We do have some outstanding questions. So

that's not completed totally yet.

And this next bullet, "can expect others in the future," let me kind of side track here into some of the questions about our North American partners.

Mexico, as I stated, has requested that we recognize them free of scrapie. We really haven't started that review. We're very unsure of the amount of information that they have provided us.

We're also a little bit leery of the fact that we send hundreds of thousands of culled ewes to Mexico every year for slaughter, but we know some of those animals are diverted into Mexico. So it's a bit hard to at least at face value take the fact that Mexico is claiming they're free of scrapie when we know that we send them large numbers of animals, and we have scrapie here in the U.S.

So that is a concern of ours, but that will be under review in Mexico's status.

Canada's status essentially is similar to ours, and at this point in time, they do have a scrapie control program. I believe people probably have seen some of the press reports. In Quebec they really had a significant scrapie problem in Quebec over the past year or so and have slaughtered quite a

few sheep.

They also are in the midst of developing a voluntary certification program similar to ours. I wasn't able to confirm if they've actually finished that and have gotten it started yet, but their industry tends to kind of run along the same lines as ours, and I know that the two industries like to coordinate things just because we do have more truly North American market. There's a lot of movement back and forth.

Let me try and clarify some of our import regs I think at this point would be a good spot for that. Traditionally in relation just to scrapie, we have not accepted sheep and goats from countries other than those countries that we defined free of scrapie, i.e., Australia and New Zealand, or countries that we considered had an equivalent surveillance system, i.e., Canada, just because that's a large volume of trade.

So traditionally that's where most of the live sheep imports have come from, have been those three countries.

Now, there was a brief window of time in the mid-'80s where we decided, okay, let's broaden this out. We had a lot of demand for additional

genetics, and we decided, okay, we would allow either genetics, i.e., semen and embryos, or in certain cases some live animals from countries that, again, either were free, and these would be mostly European countries, or countries that could demonstrate to us that they had an adequate surveillance program, and that they could justifiably say, okay, these are certified free flocks.

And we did import quite a few embryos and semen. We also imported some live animals from continental Europe, not in significant numbers though.

So let's get back specifically to Mexico. We have not brought in live animals from Mexico with one exception every year. Annually we allow in about 5,000 kid goats and lambs essentially for certain ethnic purposes, I guess, for lack of a better word, anyway, folks that like the barbecued kid goat, Cabrito. So we allow those animals in. However, they're immediately slaughtered and are not going in for breeding purposes.

Other animals from Mexico traditionally have not been allowed in because we have not recognized them free of scrapie.

So hopefully that has clarified a bit of some of the confusion earlier. Now, let me get into

some points about scrapie free flocks. What could we do for flocks in the U.S. to assure that sheep and goat materials would be scrapie free?

Again, we do have the voluntary flock certification program. We administer that program. We believe in that program, and we think that if a flock has achieved certified status, that that could be a very low risk of scrapie. Certified status means they have participated in the program for at least five years and have had no known problems for that period of time.

If we wanted to look at flocks in other countries, you could apply those same standards and say that a scrapie free flock would be one that has achieved an equivalent status in another country.

However, you could also do additional monitoring, and this is where I'm getting into a bit of a repeat of what Dr. Sutton had presented. Additional monitoring for certified free flocks could include that you're required to examine tissues from all dead animals over 18 months. If a ewe over 18 months dies, you have to look at the brain. You have to examine that brain, look at tonsils, lymph nodes, whichever other tissues you so chose.

Another option could also be to include

genetically susceptible animals as sentinels. Now, I realize we've already had a detailed discussion about genetics. There's a lot unknown about genetics, but there is some that is known, and I think if you had known susceptible animals and you put those in a flock, they could serve very well as sentinels, and if you had a problem that was not actually showing up in the flock, if you had known genetically susceptible animals, especially those with a known shorter incubation period, if the agent was there, it would be more likely to show up in those animals. So that could give you an additional assurance factor.

Live animal tests. I believe Dr. Sutton adequately covered those. Those might be a future possibility for other options, and also donor animal testing at slaughter. I'm not extremely familiar with the tissues that are used and exactly what we are talking about here, how they are obtained. However, if they were obtained at slaughter and if you could hold those tissues or hold that carcass while you did some testing, this could be another additional option, or you slaughter the animal and you pull out brain, tonsils, lymph nodes, whichever, do the testing for PrP on those tissues, and once you got negative testing on those tissues, then you could release the

carcass, release any of the other materials that would be used.

That, however, does lead to some consternation. As discussed, again, earlier in the abattoir surveys, what do you do if you have an animal that is positive on some tests and negative on others? I guess my best recommendation there -- and you all can kick this around further as I'm sure you will -- would be to go for the better safe than sorry school, and if there's any positive, then you would cancel out that animal.

Other considerations. I'll just hit these. We don't need to go into any further detail.

Closed versus open flocks. If you have a closed flock, you've got a more defined population, more control, and that would most likely be a better source.

Genetics. I won't even go into that one again.

History. You need to know have they been exposed to scrapie, possibly exposed to scrapie, even remotely exposed to scrapie.

And again, feeding practices. At this point in time we do have a feed ban in effect, but that's only been in effect for a year or so. What

about earlier, prior to that?

Now, I started off with our colleagues down under and mentioned the fact that they had very stringent import controls. They have imported sheep and goats and/or genetics in the past decade or so. However, they've done this under very strict conditions, and this is sort of a summary of those conditions.

I am putting this in because I thought this might be useful as a demonstration. Initially I thought it was a bit hard to wrap my head around this problem, to say, okay, well, this is an import solution to prevent scrapie from coming into a scrapie free country.

However, if you look at it another way, it could be similar to one point actually that Dr. Asher had mentioned initially, that this could be a way to establish from genetics a known free flock from known free progenitors. This is essentially what Australia and New Zealand were doing with these programs, and they called them their scrapie freedom assurance programs.

First of all, it started off with a quarantine isolation. You had a defined population that was going into a very strictly controlled

situation. Usually this was off shore, but if you're looking at this in more generic terms, that could be anywhere as long as you have defined isolation.

They introduce sentinel animals in there, both sheep and goats.

New Zealand, especially, never released the actual import animals. They only released the germ plasm from those animals. So they had an embryo transfer barrier essentially, but they collected both embryos and semen. Australia did the same thing, collected embryos and semen from these animals, froze those, and saved them until the end of the release.

And each of these quarantines were -- initially they were at least five years. In Australia's case they've extended that out to seven years in one instance. New Zealand has now backed off of the five years and is going with three years, but it is an extended quarantine time.

Now, significantly they did bioassays, and it varied in each import and also from each country, exactly what they were using. New Zealand traditionally used mesenteric lymph nodes, and they would pull those nodes from the imported animals themselves. They injected them intracerebrally and I believe also intraperitoneally into some of the

sentinel sheep and goats.

They have also in Australia -- they also collected placentas, and they did pooled uterine washings. As they were collecting embryos, they would use those flush fluids and, again, would inject those into the sentinel sheep and goats. Then they would examine the sentinel sheep and goats.

There were examinations also of all of the imported animals, any that might have died during the quarantine, and then they usually were never released off of the quarantine, but those animals themselves were also examined, each and every one of them, and all of the sentinels were examined.

So that is a very stringent program, but that is an example of one very tight program that could be used.

Other considerations, final points. In the information that has been sent out, it's been referenced that there are no OIE guidelines for scrapie as there are for BSE. However, I thought it would make the point that this chapter on scrapie is in development and has progressed fairly far in the process. It was up for comment again this year, which means it will at least be another year down the line. The earliest it could be adopted would then be next

May. However, it might even be beyond that.

But it is in development. It's looking better, and in this new chapter there will be guidelines for defining free zones, for establishing free flocks, and it also will include minimal requirements for effective surveillance and monitoring. So that will be a tool that we can use in the future.

And I believe that that is all that I had to cover this morning.

(Applause.)

CHAIRMAN BROWN: Thank you, Dr. Ferguson.

Is there a question or two before we break for lunch? Bob?

DR. ROHWER: I really would, with the Chairman's permission, like to badger you to find out exactly how much exposure we have had from imported animals. It sounds to me like we did import live animals from Europe or maybe even the U.K. in the mid-'80s for breeding purposes; is that correct?

DR. FERGUSON: We did not import live sheep from the U.K. in the mid-'80s. We did import cattle in the mid-'80s. All of those animals, I think -- you guys are well aware of that, but we did not import sheep.

Linda will help me out here as I screw up. We have some animals from Belgium. We currently know where those animals are and are dealing with that situation.

We brought in other -- live animals, there were not that many. Semen and embryos was more significant.

DR. ROHWER: So we've also imported animals from Europe since 1989 is what you're saying?

DR. DETWILER: Let me.

DR. FERGUSON: Yes.

DR. DETWILER: I can give you the whole rundown since this is my nemesis for the last two years here.

We imported 65 East Friesian and Textel Charolais from Belgium/Netherlands. They came in under the flock certification program. Then they announced all of the information on the BSE in sheep and goats. In that small window of opportunity after they came in, they actually came into three different flocks in the country. Two were in Vermont. One was in New York.

As soon as we were made aware of this really potential and the possibility of the feeding of the meat and bone meal, the sheep were quarantined.

None of the imported animals were entered into the human or the animal food chain.

Since that time we have attempted to buy the animals. We have gotten the ones in New York. We have not gotten the ones in Vermont. Even their progeny and their subsequent progeny are all under quarantine. They've been offered money. Basically nothing can move off the farm, even to slaughter.

If they want to go and cull, go to slaughter, we buy them. Tissues get collected, and the carcasses get incinerated. The same thing happens if something dies.

So we're in this pattern of trying to do something with them.

We've offered something similar with the germ plasm, that they would collect germ plasm. We'd, you know, slaughter all of the imported animals or all of the live animals, run all the tests on them, and if everything was clean, then release the germ plasm. So that's been offered as well.

DR. FERGUSON: But I think let me try and clarify one more time. Probably where the confusion is coming in is initially in '89 our restrictions applied, restrictions on ruminants applied to countries that had identified BSE in native animals.

Okay? The U.K., France, blah, blah, blah, that list.

So those other countries that had not identified BSE in native animals at that time, let's say, in 1992, we could have allowed live ruminants in from those countries. Now then you add our scrapie controls kind of on top of that, and until a certain period of time, we were not accepting live sheep except from those countries that I described in here.

Then there was a brief window, like '95-'96, where we changed that policy, and we did allow some of those sheep in, and that's where we allowed the group in from Belgium. At that time Belgium had not diagnosed BSE in native animals. So they were clear on the BSE front, and then we looked at the scrapie issue and said, "Okay. They've got a surveillance certification program." They were clear on that issue.

Does that help?

CHAIRMAN BROWN: It's nice to know that Yankee farmers are so stubborn.

(Laughter.)

CHAIRMAN BROWN: It would be disappointing if you had any other result.

Are there any other questions?

(No response.)

CHAIRMAN BROWN: In that case, we will break for lunch. It is now 12:15. We'll reconvene in one hour, 1:15.

(Whereupon, at 12:16 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m., the same day.)

AFTERNOON SESSION

(1:18 p.m.)

CHAIRMAN BROWN: Can the Committee please resume their positions at the front table? Again, will the Committee please be seated? We are going to commence the afternoon session.

And the first order of business on the afternoon session is to conduct an open public hearing, as we did yesterday. Dr. Freas has informed me that unlike yesterday, there are no advanced scheduled presentations from the audience or the public, but I, again, as yesterday, ask if there is anyone in the audience not on the Committee that at this point wishes to make any statement whatsoever. This is the time to do it.

(No response.)

CHAIRMAN BROWN: Seeing none, we will proceed directly to the Committee charge and presentation of questions presented by Dr. Hellman, Center for Diseases and Radiological Health in the FDA.

And it would behoove the Committee to pay attention closely to these questions which are slightly different than what you have in front of you.

Dr. Hellman.

DR. HELLMAN: Thank you very much, Dr. Brown.

And it's Center for Devices.

CHAIRMAN BROWN: Oh, what did I say?

DR. HELLMAN: Diseases. We're concerned about diseases as well as devices, but it -- no problem. It's what you had for lunch.

(Laughter.)

DR. HELLMAN: Thank you very much, Dr. Brown and members of the Committee, ladies and gentlemen.

I'd first like to thank all of the speakers this morning for uniformly excellent presentations. I did not know much about scrapie in sheep when I walked into the room. I don't know an awful lot now, but I know quite a bit. Thank you for that.

This morning Dr. Asher described the risk to humans from TSEs of animal origin. The concerns of transmitting TSEs through regulated products and the regulations -- the next overhead. Thank you -- and the regulations, policies, and practices that are in place to protect humans from exposure to animal TSEs.

Much of the concern of the regulatory agencies, as we've all heard, has focused on

protection from the TSE agent of cows, that is, BSE because of the putative etiological relationship between BSE and new variant CJD in humans.

While the risk to humans from scrapie, a TSE of sheep, and goats pastured with infected sheep is theoretical, there are certain uncertainties regarding this theoretical risk that raise concerns regarding the use of sheep and goat derived material in regulated products.

Dr. Asher indicated that such materials are used in FDA regulated implantable and injectable products either as components of the final product or as manufacturing process reagents. The FDA recognizes the importance of evolving regulatory approaches as we gain new scientific and clinical information in order to assure the safety of the products that we regulate, and that's why we've brought this issue before you today.

Since the FDA has not articulated specific criteria for assurance that sheep and goat derived materials are free of the scrapie and BSE agents when derived from animals originating from or residing in countries where one or both diseases still occur, we convened the Committee in this open public forum to aid us in its evaluation of the use of goat and sheep

derived materials in implantable and injectable medical products relative to the risk of TSE transmission.

This afternoon then I would like to present the charges -- there are two -- and the questions, of which there are two, developed by the FDA planning group to the TSE Advisory Committee.

I want to stress that the Committee is a very important resource and a vehicle for discussing the latest scientific information on TSEs and the potential risk of TSE transmission for the products that we regulate.

The Committee's first charge is to consider whether the current policies of the FDA's which rely on import restrictions and other policies of the USDA's are adequate to protect humans and animals from potential exposure to the BSE agent in FDA regulated products containing or produced with materials derived from sheep and goats originating in BSE countries or if additional precautions are needed.

The Committee's second charge is to consider appropriate precautions, including sourcing and selection of animals, veterinary scrutiny, monitoring of animals, feeding practices, and other measures that might be adequate to assure the FDA that

materials obtained from sheep and goats from the U.S. or from other countries where scrapie occurs are free of the scrapie agent and can be used safely in FDA regulated products intended for injection or implantation.

In considering their charges, there are two questions that we would like the Committee to address, and we ask that the members of the Committee be polled on these questions.

Question 1: After considering the possible risk and benefits the TSE Advisory Committee is asked to advise the FDA whether any changes in current practices are needed, and this is a change in the language as it is in the overhead to make it a bit clearer for the Committee, and I reiterate, whether any changes in current practices are needed to insure that sheep and goats originating from or residing in countries where BSE occurs would provide acceptable sources of materials for manufacture of FDA regulated products intended for injection or implantation both as components of the products and as manufacturing process reagents.

Note that sourcing some materials from BSE countries would constitute a relaxation in precautions recommended by the FDA and might be prohibited by

regulations of the USDA.

Question 2: After considering possible risks and benefits, the TSE Advisory Committee is asked whether any safeguards are needed, and this is a change in the language for clarity; again, whether any safeguards are needed to ensure that sheep and goats originating from or residing in countries where scrapie occurs are scrapie free and acceptable sources of materials for manufacture of FDA regulated products intended for injection or implantation both as components of the products and as manufacturing process reagents.

If so, what safeguards would you recommend? And this is for discussion only. The Committee will not be polled. Well, we've asked the Committee not to be polled on the different recommendations that they might consider. This is just for discussion purposes only.

To aid in your deliberations and discussions this afternoon, the Committee might consider certain points that were discussed in the topics covered this morning by our invited speakers. In addressing Question 1, you heard about the potential risk of introducing the BSE agent into sheep and goats in Europe from Professor Almond. Bear in

mind that sheep most likely were fed contaminated meat and bone meal in the U.K.

This information might be considered in determining whether and under what provisions or safeguards sheep and goats from BSE countries would be acceptable sources of materials for FDA implanted and injectable products for human use.

In addressing Question 2, you heard a great deal of information about scrapie, ranging from experimental tissue infectivity studies in sheep and goats and the potential for human and animal exposures to scrapie and other TSE agents in the U.S. from Dr. Sutton of the USDA, to FDA regulations for ruminant feed, our feed ban, from Dr. Honstead, and measures for consideration in assuring scrapie free sources of sheep and goat derived materials from countries with scrapie by Dr. Ferguson of the USDA.

Among others, measures that might be considered might include appropriate precautions regarding animal sourcing and selection, veterinary scrutiny and monitoring of animals, and feeding practices, and both Drs. Asher and Ferguson suggested certain specific measures.

They were quite similar, and I would draw your attention to the last slide that Dr. Ferguson

showed, and that contains the elements of the Australia import scrapie freedom assurance program, and whether some of those considerations could be used to establish a scrapie free program in areas or countries, regions that currently have scrapie, and these are quarantine, sentinel animals, germ plasm collection, bioassay, that is, the mesenteric lymph nodes, placenta, and pooled uterine washings, and examination of the brain of all infected animals and sentinels.

In closing, I would like to mention that in addition to addressing the questions posed, the TSE Advisory Committee should feel free to offer any other recommendations or suggestions on this issue, and to encourage open discussion, we welcome public comments on this issue, as well.

Thank you.

CHAIRMAN BROWN: Thank you very much, Dr. Hellman.

To reemphasize what we are asked to do now is to provide the FDA with a yes or a no vote with respect to whether or not any changes in current policy are needed for Question 1 and for Question 2. These will be the only two votes the panel will be asked to do.

With respect to the kinds of changes that are recommended, if they are, that will be a matter for discussion only. Unlike yesterday, there will not be polls taken of each individual member about what they suggest and the effort to arrive at some sort of consensus about what they might be.

We're doing a yes and no vote on whether any changes are needed. All discussion after that will be just discussion.

And having been stonewalled yesterday from trying to conclude any business without discussion, I will now open these two -- well, Question 1 for discussion, and also, feel free, members of the Committee, to ask of any of the speakers today, if they're all still here, additional information about any points that were not answered.

Yes.

DR. ROHWER: Can I begin by just asking for a clarification? These questions are both couched in terms of changes of existing policy, and from what I heard today in terms of FDA policy, the only policy that bears on this is the feed ban. All the other policies are USDA policies.

And is there something I'm missing here?

CHAIRMAN BROWN: I think probably not.

Will you say yea or nay?

That is correct. The FDA, aside from the feed ban policy, feed ban regulation, has no current strictures.

DR. HELLMAN: Yes. We have no consistent FDA policy in place with regard to sheep and goat derived material. That's why we brought it to the Committee. We're relying on the policies of the USDA at this time.

DR. DETWILER: Just one further --

CHAIRMAN BROWN: Linda.

DR. DETWILER: -- clarification. So is there anything in your BSE thing that -- so it's totally exempt, sheep and goat; is that correct? I just want to make sure.

DR. HELLMAN: The only one is the letter to the manufacturers of dietary supplements that Dr. Asher mentioned this morning. That did specify ovine. All the other letters specified bovine only.

CHAIRMAN BROWN: That just reminds me to say for the public record I would love the FDA to convene this Committee at some date before my relinquishing the Chair to consider the whole matter of herbals and nutritional supplements.

DR. HELLMAN: That would be interesting.

CHAIRMAN BROWN: Yes.

DR. HELLMAN: I would welcome that. I don't know about others.

CHAIRMAN BROWN: Okay. That was an aside. Yes.

DR. CLIVER: Please stay up there.

DR. FREAS: Do you want to just sit down here, Dr. Hellman?

DR. CLIVER: Or somewhere.

DR. HELLMAN: Fine.

DR. CLIVER: Whatever is comfortable, but running back and forth is going to -- okay. My question was going to try and achieve some perspective on this.

To achieve a year's supply of, say, the largest volume product that's on this list, how many animals have to die, and what is the probable shelf life of the materials?

DR. HELLMAN: I don't really think we can answer that. I don't know how many animals are used to manufacture sutures, for example, and I have no clear idea of what the shelf life of sutures would be, but I would imagine it would be fairly long.

DR. CLIVER: Okay. My point is are we looking at a situation where we couldn't grow enough

animals in Australia and New Zealand or couldn't produce the product somewhere and stockpile it for a long period. Are we running out of something urgently?

Is there anything that would drive us to try and develop an absolutely scrapie free animal population in the United States as sources of these, given that we could probably get five years ahead of ourselves and then do all of the quality assurance we wanted to insure that nothing that had to do with TSE was in those products before they were released for use?

These are things we have to think about.

DR. ASHER: Yes, all of the products for injectable and implantable use appear to be relatively limited in their use, and I suppose a legitimate solution that could be suggested would simply be to accept that the United States will be contaminated with scrapie forever, and that all animals must be considered suspect at all times.

It seems to me that there are less extreme solutions to the issue that might be considered.

CHAIRMAN BROWN: One of the products that would not have a long shelf life, I guess, I think you showed vascular grafts. That would be at least one

product that couldn't be stored --

DR. HELLMAN: Yes.

CHAIRMAN BROWN: -- for any length of time, but I don't know of any others.

DR. CLIVER: They don't freeze them or anything?

CHAIRMAN BROWN: I don't think grafting is something -- not vascular grafts, but that's just one of many, many products.

DR. DETWILER: A comment on that, versus that drastic. I just want to point out that there are a number of companies in the country that have gone to great lengths to create these scrapie free flocks, and without naming them, I mean, they've imported animals from Australia and New Zealand and put them into the program, monitor, monitor the deaths.

So if you went that drastic, okay, test everything that dies; if you went that drastic, you would preclude or exclude these companies that have spent a lot of money to assure that they have scrapie free flocks in the country, and I think that would be unduly harsh for the ones that have taken that means.

The other point that I'd like to make, and I know Dr. Ferguson showed a slide about Australia and New Zealand and a lot of brains they've looked at.

However, you know, we've been criticized in the U.S. for cattle. We looked at 7,000 out of, you know, an adult population of 40 million. They're less than about 2,000, okay?

Again, you're doing -- some of that is random source, but flocks that are monitored under such stringent things that everything that dies get a necropsy is in my mind scientifically more. You've got them more under scrutiny than from countries that you're random sourcing, although Australia and New Zealand, I don't want to say that they do.

There have been questions about even their earlier seed stock that came in because some of that did come from, you know, countries of Europe.

CHAIRMAN BROWN: What Linda is saying, in a word, is if the Committee suggests draconian measures, they might be so extreme as to completely undermine the flock certification program in this country, which is a point to think about.

Stan?

DR. PRUSINER: I would like to elaborate on what Linda said. I think she's absolutely right. I'm more comfortable with doing surveillance and doing assays and really understanding what's going on with a limited number of sheep in the United States than I

am with believing that Australia and New Zealand are scrapie free.

I want to go on record and say I don't believe it. I've never believed it, and I still don't believe, and I don't believe that you can take 100 million sheep or 50 million sheep and tell me that these animals are free of scrapie.

This comes back to my little spat with David Asher about --

(Laughter.)

DR. PRUSINER: No, I'm serious. I'm coming back to this because it's a very important point.

You can believe, as David believes, that all these diseases happen by exogenous infection or you can believe as I believe that there are these sporadic cases of CJD that we see in the United States, represent the spontaneous conversion of PrP-c into PRP-scrapie or a somatic mutation, and I would argue that happens in sheep all the time.

And I would argue that for whatever reasons, whatever the culture is in New Zealand among sheep farmers than it is in Australia, we're not seeing cases of scrapie as they appear.

And so I'm much more comfortable having

well monitored flocks of a limited size and determining that these animals to the best of our methods that are available at any given point in time are free of scrapie than I am with believing that just because the stuff comes from New Zealand or Australia that it's better.

CHAIRMAN BROWN: Yes, to introduce a slight modification from the chair, I think that that's a decent point, to be more comfortable with a heavily surveyed flock. I would think that if scrapie were existing endemically strictly as spontaneous conversion disease, that it would not be expected for flocks which are scrapie free within a year or two suddenly to come down with scrapie affected sheep after the introduction of a scrapie infected sheep into the flock.

That smells like horizontal transmission to me.

DR. PRUSINER: No, I don't mean to say that there isn't horizontal transmission. I believe in horizontal transmission once a case starts, but I'm just saying that there are spontaneous cases that begin that way, and then the infectious mode takes over, and for reasons we don't understand at all, scrapie is a much more infectious disease, a much more

infectious prion disease than CJD is among humans.

CHAIRMAN BROWN: Okay.

DR. PRUSINER: I'm in agreement with you.

CHAIRMAN BROWN: Yes. How would we explain the fact that there just isn't any recognized reported clinical scrapie in Australia? A monstrous conspiracy?

DR. PRUSINER: I think what happens is that in countries where there has been scrapie, a spare amount of it, you see this horizontal transmission going on, and the spontaneous cases represent stochastic processes where it's a relatively infrequent event, and if it's happening anywhere like the number with people, okay, at one per million in older people, age 60, age 70, many of these sheep are going to be slaughtered before that, if we ever see it.

So these are relatively infrequent events, but that doesn't mean that there aren't sheep that are harboring prions for much of their life and we just don't see the disease.

CHAIRMAN BROWN: Yes. Yes, go ahead, Dean.

DR. CLIVER: Well, this is what I was hoping wouldn't happen to the discussion because what

it essentially says is that even though maybe we're only dealing with a few sheep here, there's no such thing as a scrapie free flock no matter what you've done up to the point where you derive this material, and for expediency's sake, I wish we wouldn't get off on that because what I asked was simply to define are we talking about a few hundred sheep, a few hundred thousand sheep or how many sheep a year do we have to procure that are as scrapie free as we can possibly guarantee them to be to be able to meet this demand, and I kind of think that's where we ought to be going with this discussion rather than the possibility that somehow or other out there in the outback in Australia there's a scrapie sheep that's being eaten by dingoes or something like that and will never be detected.

CHAIRMAN BROWN: But with a view towards identifying a source or sources for the safest possible product. I mean that, I think is where you're -- no, no, no. I know you're not going to dictate the terms of safety, but the point of the question, to find out what numbers of source animals would be necessary to satisfy a supply, a need, that question implies that, therefore, you would like to kind of focus the sourcing in a way that would make you most comfortable as to its safety rather than just

have a kind of open door policy; is that correct?

DR. CLIVER: Yes. All I'm thinking is the degree of rigor that can be applied depends to some extent, one, on how many sheep are we talking about and, two, can we prepare the product well in advance to cushion ourselves against sudden surges in demand and also to allow plenty of time for quality assurance testing before any lot is released.

CHAIRMAN BROWN: Yes.

DR. CLIVER: This is the way FDA operates.

CHAIRMAN BROWN: And FDA cannot now furnish those numbers. So we're going to have to at least take our votes without the numbers.

Bob.

DR. ROHWER: First, I'll begin with Dr. Cliver's point, and that is that it depends a lot on what you're talking about. There may be very high exposure parenteral products or devices that are developed that are used on a very small scale such that the sourcing needs can be met by a closed flock, and I believe that it is possible to create closed flocks or herds of animals that are very, very safe.

But, on the other hand, when you have something that's made in bulk, you may have to go to the bulk slaughter in order to get enough of it to

satisfy the mass quantities that are required for your particular market, in which case people may have to go offshore to places like Australia and New Zealand to get something that meets a higher standard on a higher scale.

I agree with Stan. I'm not convinced either that surveillance is good enough in Australia and New Zealand to know that they've never had it or it's not happening at some low rate there, but it's clearly better than it is here.

Finally though, in terms of the certification program which is what I really wanted to address my remarks to, I think that's a fine effort on the part of the USDA to try to prevent the spread of scrapie in this country and perhaps I would hope that ultimately their goal was to eliminate scrapie by this program.

I know that the stated intention earlier when it was first formulated was that there'd be enough economic incentive for joining the program that it would force people out perhaps who were operating at a lower standard, and eventually it would evolve that the entire sheep husbandry program would be brought into this certification program and we'd get rid of scrapie that way.

At two percent, I don't think we're even close or maybe even moving in that direction, but the other thing about the scrapie program as formulated by the USDA is that it's directed towards food safety and not parenteral uses of the products from these animals, and personally I think that the FDA should have their own standards and should develop their own standards for sheep for products that are going to be used parenterally in human beings and for human health from these animals, and I think they have to meet an even higher standards, and I would think that the minimum standard would be a standard more in line with the types of quarantine and isolation that the Australians and the New Zealands are employing in their programs to protect their countries from the import of scrapie.

And those same types of programs could be instituted here for developing closed herds with very high level of security starting perhaps with imported stock from New Zealand and Australia as a beginning.

CHAIRMAN BROWN: Peter.

DR. LURIE: I guess I'm still left with a number of questions about the devices themselves, which are really the issue here. How commonly are they used? What are the alternatives to them?

Some companies evidently are able to source these implantable and injectable products from non-BSE countries, setting aside scrapie for a moment. I feel like we're missing a lot of information about the production of these things. Can you fill me in at all?

DR. HELLMAN: Well, I can speak about the sutures and the vascular grafts to some extent. I'll start with the vascular grafts.

Both bovine and sheep collagen are used for vascular grafts. We have one product. With regard to the sutures, there are 14 manufacturers of cat gut sutures, but I understand that there are other materials that were used as suture material in addition to the "cat gut" sutures.

I can't tell you how widespread the usage is compared to the other forms.

With regard to the biologicals I believe David can speculate about that. I don't believe either of us have too much information about the drugs.

DR. ASHER: Yes, these are all limited, very limited use products, and the issue at least at the moment would not be shortage of supply offshore. What we had hoped to get was some idea about policies

that would make it possible to consider safe sourcing from any country, of course, but particularly from the USA.

But could these all be sourced at the moment from Australia and New Zealand? Quite possibly.

CHAIRMAN BROWN: Bruce, you had your question?

DR. EWENSTEIN: Yes. I just wanted to bring the Committee back to the kinds of components that were mentioned at the very beginning of the day, and these include components that are active ingredients in drugs or biologics directly versus those that are used in the manufacturing process.

Now, I mean, I'm not sure how much of a distinction we should make, but it seems that the material that's used for affinity chromatography in the manufacturing process would be of less risk if one had to draw a line somewhere than those that are going to be directly injected into patients.

CHAIRMAN BROWN: Dave.

DR. ASHER: Yes, and there's a precedent for that view in this Committee, which looked at the use of human blood derivatives as manufacturing process reagents and felt less concerned about the use

for manufacturing than when the same ingredients were used as excipients or active ingredients.

CHAIRMAN BROWN: Ermias.

DR. BELAY: I'm not absolutely clear about the current practice. Where is this product sourced from? Are they all coming from within the country or are they imported from other countries?

And if they are imported, where are we importing them from?

DR. HELLMAN: You're asking about the suppliers of the materials that are used in the manufactured products. I can't tell you who the suppliers are. If I had to venture a guess, I would say that it could probably be sourced from the U.S. or it could possibly be that Australia and New Zealand, if we went to a scrapie free source, could supply it as well.

But I just cannot give you any details about the suppliers.

CHAIRMAN BROWN: Yes, in defense of the non-information coming from the FDA, if you don't have any regulations, there's no point in knowing where things are coming from. So it may be that we will not be getting answers to many of the questions that are occurring.

Raymond.

DR. ROOS: Just talking about sheep and scrapie, it is true that we have no data that suggests that scrapie can be transmitted into humans and to prion disease.

Nevertheless, I think it would clearly be valuable from a public health point of view to have scrapie free reagents for, for example, gut as well as vascular grafts, if we could achieve that.

We're told that Australia and New Zealand have very low incidence of scrapie. On the other hand, I do agree with Linda. I think it may be at this point we should promote and encourage scrapie free flocks here.

So I'm wondering whether one couldn't make regulations encouraging at least initially in use of certified flocks in the United States that are scrapie free or scrapie free countries or other countries that have a certification program like ours do with respect as -- for their use for products, such as gut and vascular grafts.

With respect to bovine derived products for the gut and vascular grafts and so forth, it seems to me we kind of addressed this at a previous --

CHAIRMAN BROWN: No, this isn't the

question.

DR. ROOS: Okay. I get a little confused.

CHAIRMAN BROWN: No, it's scrapie. It's sheep and goat derived.

DR. ROOS: Okay. Sheep and goats.

CHAIRMAN BROWN: Sheep and goat derived products either from countries that have BSE or countries that don't.

DR. ROOS: Well, what I'm saying is that it seems to me that we should promote the certification program here and allow use of material from these certified flocks, as well as other countries that have comparable certifications or scrapie free counties.

CHAIRMAN BROWN: Yes, and that's a good point. We've not obliged to say, "Here are nine possibilities. We pick number three." What you just said, it's not an either/or. It's, yes, we might want to recommend sources for these materials from animals that are as likely or which are likely to be scrapie free in one way or another, whether it's certified or whatever. I mean that would be a kind of a position that we would suggest that the FDA take, that they take care to get scrapie free sources.

DR. CLIVER: In that connection, I think

that another item of policy is that the source of the raw material be determined. We're being told now that that's not currently done, and so if you're going to stipulate, then you've got to have some kind of a reporting stipulation built in as well so that when a lot is set up for approval that you know where the raw material came from.

Additionally, it seemed as if from what we were just discussing, that maybe the most ephemeral product was this vascular transplant thing, and then I think I heard something about reconstituted collagen, and that sounds rather like what they do to make sausage casings these days, which suggests to me that maybe the shelf life of these isn't that bad either.

DR. DETWILER: One comment.

CHAIRMAN BROWN: Oh, Kiki, did you want to respond to that?

DR. HELLMAN: Yes. I just wanted to say that devices can be regulated under the 510(k) process or the pre-market approval process. Oftentimes for products that are through the 510(k) process, we do not necessarily know the suppliers or the source because it's not necessarily required. For those under the PMA process, which would be vascular grafts,

we would know the supplier.

So it depends on the provisions of the regulations as to how much information we can require of the manufacturer. However, is a decision is made that even for sutures it's desirable to know the source supplier, then there may be ways that we could work with that.

CHAIRMAN BROWN: Yes, Dave.

DR. ASHER: Yes, for biologicals the source has to be known. When I was -- the point I was making is that there was no formal policy concerning the source.

So, for example, recently the sponsors of a product found it convenient to satisfy concerns about safety by sourcing from Australia or New Zealand rather than bothering to try and figure out what to do in the United States.

It was for that reason that we thought it would be useful to consider criteria that would assure a safe source in some way other than going to a putative scrapie free country.

CHAIRMAN BROWN: Linda?

DR. DETWILER: One of the things I'd point out is that currently the USDA prohibition on the importation of most ruminant products would prevent a

lot of these from coming in, especially in like the casing form type because that's specifically in the regs

Where we get into problems, if it wasn't labeled as such that somebody would recognize it as ruminant material, and then there's also cases where it would come under special permit, and most of that is for some scientific or research purpose.

DR. HELLMAN: May I? We just did receive some more detailed information about the drugs, and the approved drugs have sheep wool from New Zealand. There are two of them. Of the investigational drugs, we're considering only injectables and implantables. One sources is from Argentina. Two sources, from Europe, nonspecified which country.

CHAIRMAN BROWN: You have a runner going back and forth to home base hot off the press?

DR. HELLMAN: Carol Vincent just handed me this.

CHAIRMAN BROWN: Okay. Peter.

DR. LURIE: Kiki, if I can just rephrase what you said, what I think I heard you say is that there are medical devices being implanted in people in this country and you don't know what the source of it is in some cases?

DR. HELLMAN: I did not say that.

DR. LURIE: Can you correct me then?

DR. HELLMAN: What I said was that there are two regulatory modes, if you will. There are products that are 510(k) products, which means that they're rendered substantially equivalent to products that were approved for marketing before the medical device amendments came into practice.

Then there are products that are considered that both safety and efficacy must be shown and that you must have clinical data, and those are pre-market approval.

And for those types of applications, one certainly knows the supplier. For the others, since they are substantially equivalent to something that was marketed before the amendments came into effect, we do not always know the supplier, and it's up to the reviewer to find out from the supplierif it is a particularly sensitive product or it is made with particularly sensitive materials.

As, for example, when we had the BSE problem, we inventoried all of the products in the center with regard to their animal tissue of origin, and we then recommended, many times reviewers calling individual manufacturers, recommended that they

consider sourcing from suppliers that did not have cases of BSE if, indeed, they were sourcing from a supplier that was using cows from a BSE country.

So in the latter case, we definitely know the supplier. In the former case, the 510(k), we don't always know the supplier. If there is a problem, there are ways that we can find out.

DR. LURIE: Okay. That's my point.

DR. HELLMAN: Does that clarify it?

DR. LURIE: Yes. That's not inconsistent with what I said. There are some devices in the 510(k) process for which you might not learn, perhaps because you choose not to, what the supplier was or from what country they were sourcing.

DR. HELLMAN: Certainly if there is a question with an adventitious agent that may be potentially infectious for the recipient, we take measures to assure ourselves of the supplier and the source material.

CHAIRMAN BROWN: Let me try something here, and that is this. For a little bit, could we refocus on just any missing information that would require -- that you would require before making a yes or no vote on these two questions rather than a discussion of what kinds of -- what kinds of different

sourcing, you know, the details?

If there is anything that you would like to know in order to be able to say yes or no to the two questions, let's ask those questions and then take a vote, and then we can have lots of discussion about anything at all.

Bob.

DR. ROHWER: I would like to make a point before I make a vote because I think it would influence the vote. So this is not a request for information. It's just my opinion of vulnerabilities that I see in the scrapie flock certification program, which I would want to see rectified before those animals were considered closed enough and safe enough for the sourcing of parenteral devices or drugs.

And the main vulnerability I see in that program is the opportunity to introduce scrapie via new animals and new breeding stock, and I think that should be, for drug and parenteral use, it should be closed off. It should be genetics can be introduced by embryos and semen only, but you don't introduce new animals into a flock like that once you have it established.

And the reason I say that is that there's just too much history of scrapie showing up in strange

places like pastures where scrapie has been before but scrapie free flocks have been put on those pastures. It's very, very hard to get rid of this.

The idea of introducing susceptible sentinels for monitoring scrapie also bothers me a lot because it seems to me like that's just asking for it. There's the opportunity to introduce an animal that's got scrapie without knowing it.

The other things that need to be addressed, of course, are feed. It should be specified that only vegetable feeds are allowed for a flock that's going to be producing medical material.

Another point is isolation. These animals should be isolated from all other contacts with sheep and probably bovidae and cervids.

And those are the three main vulnerabilities I see in the program right now.

CHAIRMAN BROWN: And these are details about -- I don't think --

DR. ROHWER: Well, they're details --

CHAIRMAN BROWN: -- they'll influence the yes or no. What you're saying is it's a good idea.

DR. ROHWER: No, it influences my vote because what I -- because I think these things are needed, I have to say, no, I don't think -- well, I

can't remember if this is a negative.

I think that the FDA does need to set their own standards.

CHAIRMAN BROWN: Okay.

DR. ROHWER: They shouldn't ride on what they've got.

CHAIRMAN BROWN: Right, and that would be a yes.

DR. ROHWER: A yes. Right, okay.

CHAIRMAN BROWN: I may try and deceive you later depending on, you know, how --

(Laughter.)

CHAIRMAN BROWN: Larry.

DR. SCHONBERGER: I just want to clarify again. The current safeguards, do they prevent the sutures, the vascular grafts from coming from sheep or goats in BSE countries because of the ban that currently exists?

I thought I heard that you were saying, Linda, that it may not even be recognized as a ruminant product possibly or could get miss --

CHAIRMAN BROWN: Yes, Linda. What does the USDA allow in within the context of these questions?

DR. DETWILER: Actually --

CHAIRMAN BROWN: Or maybe I should say what do they exclude.

DR. DETWILER: Yes. Actually I'm going to kick that to my import-export colleague over there.

CHAIRMAN BROWN: Okay.

DR. DETWILER: Because she would have the real specifics.

CHAIRMAN BROWN: Ultimately we're going to come down to deciding because the FDA is our host what we recommend to the FDA, and what the USDA does is, in fact, irrelevant to what we're going to recommend. It really is, but it would be very nice to know what the USDA does not allow presently.

DR. FERGUSON: Okay. I think it might be easier for me to say what we will allow in, and that's as the reg is written, and as the reg is currently written, we have exemptions. Essentially it is saying no ruminant or ruminant products from all of Europe, and the exemptions are what we have determined, and they are widely accepted not to be a risk.

CHAIRMAN BROWN: And those were the ones that John showed?

DR. FERGUSON: Those are --

CHAIRMAN BROWN: Gelatin, milk, blood. No?

DR. FERGUSON: No.

CHAIRMAN BROWN: All right.

DR. FERGUSON: That's their -- some of them are the same, but some of them are not.

CHAIRMAN BROWN: Okay. What are yours?

DR. FERGUSON: Milk and milk products, hides and skins, semen, tallow, and then certain blood products used in microbiological media, you know, where you've got -- it's essentially a processing agent, and it's not coming into direct contact.

CHAIRMAN BROWN: Are any of these products under the purview of the FDA? That is, you've described a number of products or a number of items, materials, some of which may not be relevant to an FDA guidance.

DR. FERGUSON: Well, I think where a lot of the confusion comes in, and I think this is what Linda was referring to, is how these products are manifested when they come. You know, it's in a container or pallet that's arriving at the port, and our inspectors, many of them are very good, and they know how to flag these things on a manifest or on a declaration as a ruminant product, but some stuff they very well might not know, and that would be some of these more derived antibodies, that type of stuff that

might be a bit iffy.

Now, we think we're getting most of them, but that's where the lines cross, and where it gets confused.

CHAIRMAN BROWN: That is just one more layer of confusion. I mean if I'm -- that's not exactly what I asked, but now if you're talking about incompetent inspectors who look at a pellet when it comes in the port, and don't know what it is, good Lord, huh?

DR. DETWILER: No, Paul, wait. I've got to correct that because it's a pallet, and like say a drug comes in, okay? A manufactured drug comes in at the port, and it doesn't specify that it contains sheep or goat material. It's labeled as whatever the name of the drug is.

Well, no way, unless you had some kind of ingredient, would they know that that's how it was manufactured, and that's where we can have it where they have are reg that approves that drug with this sheep or goat material in there, and theoretically our reg should keep it out, but there's no way to know that's what was in it.

Does that clarify it more?

CHAIRMAN BROWN: Well, it clarifies it to

the extent that I'm a little more uncertain about import screens, shall we say? I mean if a pallet is coming in and it contains -- I mean, and let's say it's -- I don't know -- it's labeled what, albumin, without specifying that it's albumin from a cow that died with a neurological disease in England. No, that would concern me a great deal.

DR. HELLMAN: If I may.

CHAIRMAN BROWN: Kiki.

DR. HELLMAN: Of the items that Lisa tallied off, the ones that would find themselves in FDA regulated products would be tallow derivatives and those for microbiological media, if they were for in vivo use. And when we had our Advisory Committee and we discussed tallow derivatives --

CHAIRMAN BROWN: Yes, Yes.

DR. HELLMAN: -- if you recall, we considered that with the processing that the tallow would have to go through, we needn't worry, quote, unquote, about tallow derivatives.

CHAIRMAN BROWN: Yes, Yes.

DR. HELLMAN: So it's the microbiological media if it finds itself into an in vivo biological.

CHAIRMAN BROWN: Right. So, I mean, this is beginning to clarify things. Of the list that you

gave us, tallow, which the Committee has already considered and the FDA has our recommendations on it, and the other one was microbiologicals did you say or biologicals? What?

DR. HELLMAN: Elements for microbiological media.

CHAIRMAN BROWN: Microbiologicals.

DR. HELLMAN: And if -- if -- if the microbiological media is used to manufacture biologicals for in vivo use, then that would be a consideration. So from that list, that's probably the only one of concern.

CHAIRMAN BROWN: Right, and so the microbiologicals could come in on a pallet rather than a pellet and not be specified as to source, that is to say, coming from a ruminant?

DR. DETWILER: Because Carol Vincent just told me that one of the things is doxirubicin.

CHAIRMAN BROWN: Yes.

DR. DETWILER: And that would be one of the examples that that's how it would come in, labeled "doxirubicin."

CHAIRMAN BROWN: Okay. Without specification as to source?

DR. DETWILER: Well, I don't know with FDA

-- with labeling, but that's possible, yes, for us.

CHAIRMAN BROWN: Is that right? Doxirubicin is a wool derivative?

DR. ASHER: Yes. It contains a component that's noted to be extracted from wool, and we were less concerned about wool than we were with things like tissues.

CHAIRMAN BROWN: Okay. Other comments? Ray. Oh, excuse me. Why don't you go ahead?

DR. FERGUSON: Yes. Let me just add a couple of additional clarifications. One that Larry asked me here kind of on the side and just to clarify, casings and collagen, that type of stuff is restricted under our current regs You know, it is prohibited.

Then also the point where you were using the example if something came in and it's labeled as albumin. That would be flagged for our inspectors, and somebody would be asking, you know, "Well, what is this? Is it bovine serum albumin?" They would be querying for further questions, you know, and a determination would be made.

So those types of things probably would be caught. It's the finished product, doxirubicin, coming in, you know, in a container that would be an issue.

CHAIRMAN BROWN: Again, further questions that will allow us to make yes or no votes on the issue of whether we want current practices, we recommend current practices either be left intact, and the current practices essentially are carte blanche. That is, there are no regulations, or whether we would recommend that some kind of oversight regulations be instituted?

Bob.

DR. ROHWER: A clarification. So if something like doxirubicin is imported and it goes into an FDA regulated product, the manufacturer nevertheless has to identify the source of the doxirubicin to the FDA, do they not? So you will know.

DR. ASHER: Yes. It's from New Zealand.

CHAIRMAN BROWN: Ray?

DR. ROOS: Yes. I hate to beat this to death, but so just getting back to gut sutures and vascular grafts, could those be received from BSE countries, sheep derived, and escape our scrutiny at the moment?

DR. FERGUSON: No, they really couldn't. Those are controlled under ours. We have informed our inspectors of specific things like that. So, no,