Cross blood, and so, individuals that they might be administering a transfusion of blood that satisfied the criteria of the FDA but not the American Red Cross and I think that is an issue and it is one that I could see might be troubling to the transfusion recipient as well as the blood bank itself and I just guess I was interested maybe in American Red Cross' comments here and maybe FDA just because I think there are tensions related to that.

Now, I am sure that there are instances in which medical and lay group come up with guidelines that might differ from the FDA saying that a priori that should not be, is not appropriate in given circumstances. This particular one I guess both of these guidelines are based on predictions of safety versus availability of the product and maybe they are using pretty much the same data and so forth and for that reason I guess I would have hoped that there could have been some agreement in order to decrease confusion and maybe those tensions.

DR. BOLTON: Could we get a comment from the FDA on that?

DR. SCOTT: I just want to make the point that it is certainly permitted for blood establishments to have more restrictive criteria than FDA recommends, and I think that we all tried to come to some kind of agreement on this, and we have differences of opinion in particular about the

effects on supply, and that you may wish to comment further but we just haven't been able to come to a position that we can easily agree upon.

MS. FREDRICK: Yes, if I can address the first, now, we have only been doing this for about a week, but this has been the smoothest implementation of a new policy that I can recall and to my knowledge there have not been any major donor issues in terms of their confusion, quite the contrary because I think we have gone to great lengths in educating the donors.

The other thing I would offer, and I don't know, maybe Jeff McCullough knows the data. The Red Cross for another issue entirely back I think in the seventies or eighties, Bill Sherwood had done a study on how many donors actually cross over with even the Red Cross system, donate in Madison and donate in St. Paul for entirely another reason and as I recall the data is extremely small in terms of the number of donors who actually go through and donate at two places. So, I am not sure that this is really an issue for donors.

I think the other thing is we have been for decades working with different blood donation records. So, when I go into New York Blood Center, for instance, they have a totally different form in many ways that I go through then when I go down to Philadelphia.

We have had differences; for instance, recently we have just reviewed our antibiotic deferrals and blood centers differing in cancer and antibiotics. At the very least we have to meet FDA agreements but generally there has not been confusion with donors.

DR. FITZPATRICK: I am in the somewhat unique position of running both the recipient and the donor side of the house. We run transfusion services at 121 facilities and we collect the blood for those transfusion services. Our dilemma prior to your last meeting was whose guidance were we going to follow because there was such a wide disparity between what was being implemented by the Red Cross and what was the recommendation from the Committee and the FDA.

We worked I think diligently and hard with all organizations to try to facilitate and help come to a single criterion, but it was actually Dr. Williams and the FDA who brought the information to the table that we needed to allow us to be able to tell our recipients and our donors that we were following what we felt the safest criteria for them because I have not only a medical but a political factor I have to answer to, and that was when using, say modeling methods the Red Cross criteria were evaluated and the FDA guidance document was evaluated and depending on where you round the figures there is a 1 to 3 percent difference in the reduction of the theoretical risk in following either

FDA or ARC's criteria.

That very eloquent presentation and your recommendations allowed me to go to my political bosses and say that we can implement the FDA criteria even though there is a difference between that and the Red Cross and the fact that over 45 percent of the blood being collected is collected under different criteria and that we can tell our patients in our facilities that sometimes we don't meet all our requirements and we have to get blood from a civilian agency, and that could be an ABC agency or it could be a Red Cross agency.

Everyone is following the criteria to reduce the theoretical risk as much as possible given their interpretation of the impact on supply, and that was acceptable to both our hospitals and our political and our medical consultants and only time will tell the result of that, but that is where we were and that is how we got to where we got to.

DR. BOLTON: Dr. Bianco, do you have something that is dramatically different than what has already been said?

DR. BIANCO: It is not dramatic, but it is different.

DR. BOLTON: Keep it brief.

DR. BIANCO: I want to thank Dr. Roos for raising

that very important question. The second thing, the issue is not so much the confusion of donors. There is an issue of decision making process. Those are public health decisions. I think that what has been established here by this Committee, by FDA, those numbers were achieved in the studies that were done before in the modeling that showed that adding from 6 months to 5 years made very little difference. So, this was a reaction to the decision-making process. I wish we would all be able to follow the same rational decision-making process and have a single criteria for a major public health issue.

Thank you.

DR. BOLTON: I guess I will wrap up the discussion by saying that I agree. I think it would be nice to have a uniform set of criteria for this, but I think that the two sets of criteria can co-exist, and the fact that these criteria probably will evolve over time, it is not a disastrous circumstance to have these slightly out of phase and so I hope that we can continue to have a safe and adequate blood supply going forward even with these different sets of criteria.

What I would like to do now is take our break. It is now, I have ten-forty-eight. Let us round it to ten-fifty, a 10-minute break. Come back at 11 o'clock and begin our Topic 2 only one-half hour late.

So, I will see you back here at 11 o'clock.

Thank you.

DR. FREAS: If you are speakers for the morning's agenda and you would like to get your slides, would you please to the audiovisual booth?

Thank you.

(Brief recess.)

DR. BOLTON: Sheila Longford has asked me to let the FDA panel members know that there is a special table set up in the restaurant for us. So, as you enter the restaurant just identify yourself as an FDA TSE Advisory Committee member and they will usher you to the special table which is not serving Kobe beef.

We are beginning Topic 2, discussion of the amino acid sourcing and production and the theoretical risk of transmission of the BSE agent through their use in biopharmaceutical products.

Our first speaker is going to provide an introduction overview and that is Dr. Gerald Feldman form OTRR and CBER.

Dr. Feldman?

DR. FELDMAN: Good morning. I am Gerald Feldman from the Center for Biologics Evaluation and Research, and I would like to thank the members of the Transmissible Spongiform Encephalopathies Advisory Committee, the speakers

and the audience for participating in this section of this morning's TSE Advisory Committee meeting.

This meeting of the TSE Advisory Committee continues the agency's process of assuring the safety of FDA regulated products with regard to the risk to the public health posed by transmissible spongiform encephalopathies.

The potential for contamination of biological products with the agent that causes bovine spongiform encephalopathies or BSE has been a concern of the Center for Biologics of the USFDA for many years.

In 1990, FDA intensified its review of new product applications for human medical products derived from or containing bovine sources.

FDA recommended to manufacturers of these new products that they not purchase as components animal tissues or products that originated in a country where native cattle had been diagnosed with BSE.

In 1993, and again in 1996, FDA issued letters to the manufacturers of drugs, biologics and medical devices advising them that in the manufacture of FDA regulated products intended for human use they should not use materials derived from cattle born, raised or slaughtered in countries where BSE is known to exist. Again, in 2000, CBER reissued the same advice to vaccine and other biological manufacturers regarding bovine materials from countries

having or at serious risk of having BSE.

In recent years the TSE Advisory Committee has reviewed the relative risks of several processed components. For example both tallow and gelatin have been subjects of advisory committee review.

In 1997, the TSE Advisory Committee recommended that no bovine-derived material from a country with BSE be a source for gelatin used injectable, implantable or ophthalmic products.

The Committee further recommended that for oral and topical use safe sourcing of gelatin be implemented. When manufacturers were asked to identify all animal drug components used in their manufacturing processes most manufacturers took into consideration process components such as gelatin and tallow, but very few considered amino acids which are the building blocks of all protein.

In this meeting we will focus our attention on amino acids which like gelatin and tallow are processed ingredients. Unlike gelatin and tallow, however amino acids have never been discussed in an open forum and very little has been publicly presented regarding the manufacturing of the product or product polycontrols involved in their production.

In considering the safety of any bovine drug component three things must be taken into consideration, its

method of production, the sources of raw materials used and its ultimate use.

Generally speaking there are three methods of production of amino acids as listed here. There is microbial fermentation, chemical synthesis and either chemical or enzymatic hydrolysis and there are many possible sources of tissue as listed here. You can have vegetal proteins which are the source of the raw materials or animal proteins either avian feathers or various mammalian tissues.

FDA has not conducted a rigorous assessment of the manufacturing process for amino acids and therefore has not considered whether or not these ingredients can be subject to a different level of control than we currently have.

One purpose of this meeting is to obtain information about the sourcing of raw materials, the range of manufacturing processes and the dynamics of the market in order to better assess product safety and to consider adequate and appropriate controls for domestic and imported products.

Amino acids can be used in a variety of ways in the pharmaceutical industry. Broadly categorized they fall into these three areas. They can be used as active ingredients, as excipients or as reagents.

Amino acids are considered active ingredients when they comprise the drug itself. These can be oral dosage

forms of a purified amino acid or infusion bags or bottles containing large volumes of amino acids and/or electrolytes for nutritive or reconstitutive purposes.

However, when used as active ingredients amino acids are regulated by the Center for Drugs and specifically for amino acids used in this way the Center for Drugs has implemented a strict policy which subjects amino acids to the guidance issued by the agency for other high-risk bovine-derived materials, namely the materials that come from cattle born or raised or slaughtered in countries where BSE is known or thought to exist, cannot be used in the manufacture of FDA-regulated drugs intended to be used by humans or animals and thus in accordance with this 1996 FDA policy there are no bovine-derived amino acids from BSE countries used as an active ingredient.

However, in this context there are no restrictions on other ruminant sources or from animals that come from non-BSE countries.

Amino acids can, also, be used as excipients added to the final preparation for a variety of purposes such as providing a buffering salt for a particular pH or as a stabilizing agent to prevent the degradation or oxidation of the active substance and finally, amino acids can serve as reagents in the production of the final product. Thus, they can serve as buffers used to purify the active drug

component or as components involved in the synthesis of the final product, either by chemical means such as peptide synthesis or by biological means as components in the culture media used to make biopharmaceuticals such as recombinant DNA derived drugs, vaccines or cellular therapies.

For use as excipients and reagents there are clearly no restrictions on the source of amino acids. Furthermore there is little published or public information regarding the materials from which amino acids are derived commercially or the processes used to manufacture and purify them.

At issue is the potential contamination with the BSE agent of bovine-derived source material used in the manufacture of US licensed biopharmaceutical products and possible exposure of product excipients that might result through the use of amino acids of bovine origin if these were obtained from animals infected with the BSE agent.

When contacted for information on the source of the amino acids used many pharmaceutical companies initially responded with surprise that amino acids were considered to be animal derived. More often than not they could not determine the source of amino acids used referring us instead to the suppliers of raw materials or growth media.

Some pharmaceutical companies felt that our

requests were misplaced since of course, amino acids are considered safe. After all they are isolated by acidic enzymatic hydrolysis of proteins and are subsequently purified by chromatographic methods or they are subject to a multitude of chemical reactions and purification steps as it goes from the raw material to the final product.

When suppliers were directly contacted for information regarding their sources of amino acids the responses demonstrated the complexity of the market. As illustrated by these few examples, amino acids can be obtained from multiple manufacturers and manufacturers could have multiple methods of production for the same amino acid.

In most cases the supplier had no further information beyond what is listed here, the company or companies from which the amino acids were purchased and whether or not they were known to be animal derived with no information regarding the type or source of the animal, and so, we contacted the manufacturers of the amino acids themselves, and when they were contacted directly the agency received conflicting information on what raw materials were used and from where they were sourced.

Because methods of production and the sources of raw materials are so varied and uncertain representatives from two of the larger manufacturers of amino acids accepted our invitation to present descriptions of their

manufacturing processes and will hopefully provide further information on the production and purification of amino acids.

After their presentations we ask that the TSE Advisory Committee consider the safety of amino acids produced from ruminant-derived materials from BSE and BSE-risk countries with regard to the likelihood of transmission of the BSE agent.

We, also, ask that the Committee consider the appropriate precautions that should be taken regarding the use of ruminant-derived amino acids in the manufacture of biopharmaceutical products and finally we ask the Committee to consider the potential risks and possible actions to be taken with regard to licensed, approved or investigational products that may be affected, and so we have provided the Committee with three specific questions to focus on.

One, does the Committee think that the current manufacturing and processing control methods utilized by the manufacturers of amino acids minimize the risk to allow bovine-derived amino acids from BSE countries to be used as reagents and excipients for the production of pharmaceutical products?

Two, if not, does the Committee feel that there are any circumstances where the risk/benefit ratio would still be in favor of a subject receiving a product where

suspect amino acids have been used in its manufacturing process?

And finally, if not, does the Committee think that the current manufacturing process and control methods utilized by the manufacturers of amino acids minimize the risk to allow other ruminant-derived amino acids from BSE countries to be used as reagents and excipients for the production of pharmaceutical products?

And with that I would like to end and open it up to any questions and thank you very much.

DR. BOLTON: Was it intentional that you left off Question No. 4? It is in our handout.

DR. FELDMAN: It is in your handout but the presentation that I provided just now was modified as of 9 o'clock this morning. So, there have been a few changes since the handout was made. We purposely left out the fourth question, but the Committee is welcome to bring it up if it feels it is important.

DR. BOLTON: Okay, Peter?

DR. LURIE: If I understand correctly you are interested in the Committee's comments, questions in response to questions regarding the reagents and excipients, is that correct?

DR. FELDMAN: That is what we are interested in now. If you wish to consider the use of amino acids as

active ingredients or feed additives or whatever else, we would be very interested, but the questions we put forth to you now are exclusively on excipients and reagents. That is one of the main problems that we are facing now in the Center for Biologics.

DR. LURIE: I guess one reason for that as opposed to looking at the active ingredients themselves is the assumption that the companies are complying with the various guidances that the FDA has put out. Is that right?

DR. FELDMAN: For active --

DR. LURIE: For active ingredients.

DR. FELDMAN: Yes, they are. The Center for Drugs requires that a manufacturer provide a master file for each amino acid that it produces that is used as an active substance, and that master file goes into great detail regarding the manufacturing process. Those countries, the sites of those countries are visited on a supposedly biannual basis by our inspectors to assure that the process is according to the master file. So, I believe that the Center for Drugs is assured that everything is kosher under those circumstances.

DR. LURIE: The reason, obviously, you asked us this because we have been through all this with vaccines before and so the reason is that things were not kosher and so, am I correct in understanding then that FDA believes

that things are, you know, whatever words, adequately clear with regard to active ingredients that that has not been brought up in the way that it was for vaccines?

DR. FELDMAN: I don't want to speak for the Center for Drugs and I don't know if there is a representative from CDER here. I was assured that there would be, but I was assured by representatives from CDER that there is only microbial fermentation processed amino acids or chemical synthesis derived amino acids used as active drug substance. That was an assurance by the Center for Drugs, but again, that was to me. I would rather that you hear that from them rather than me.

DR. BOLTON: Is there a CDER member here to provide us that information?

DR. WU: Yes, I am from CDER.

DR. BOLTON: Please come to the microphone and identify yourself?

DR. WU: I am from CDER and the information we are going to be declaring in follow-up to the DNA mechanisms. So far the only animal sources we have encountered is coming from across countries. So, we follow up that to prevent the animal sources from being used and selecting ingredients to deal with mechanisms.

DR. FELDMAN: I should point out that that is Dr. Wu from the Center for Drugs.

DR. BOLTON: Thank you. Dr. Roos?

DR. ROOS: Maybe I need some clarification here. So, you are talking about vaccines, is that right?

DR. WU: Drugs.

DR. ROOS: So, let me just follow-up I guess on Peter's question with respect to vaccines and what their status is with respect to the use of amino acids that might be bovine derived either as excipients or as reagents and what the status is now as well as FDA guidelines.

DR. FELDMAN: Dr. Egan, would you like to address that question?

DR. EGAN(?): Do you want to know currently the guidance with regard to amino acids? Is that your question, Jerry?

DR. FELDMAN: Yes, it is not my question, but --

DR. BOLTON: It is Dr. Roos' question for vaccine production as reagents really cell culture reagents I assume.

DR. EGAN: There has been no explicit guidance either with regard to amino acids used for the manufacture of vaccines either as excipients or as reagents used in culture media.

When we had the meeting that Dr. Lurie is referring to a year ago we had said that at that time we were not considering as high risk the amino acids that had

been used in production.

DR. BOLTON: I just want to comment. I think that is really why we are discussing the topic here today is because potentially animal-derived amino acids may be used as either excipients or reagents in many products but especially vaccines and so now I think we need to have the presentations to find out how these products are produced and what the possible risk might be if the tissues themselves were sourced from bovine materials from BSE countries or other ruminants.

DR. ROOS: Just to follow up I thought there had been some recommendation to exclude all bovine-derived products from vaccines. Am I wrong about that?

DR. EGAN: All bovine products from BSE countries, yes, that is correct but you know we have a number of issues, for example, where we have working seeds, viral seeds or bacterial seeds or sow bags that in the past had been using these materials and what to do with those and that would still be an issue.

DR. DE ARMOND: I guess I need some clarification and perhaps we will learn a little bit more about it. What is the percent protein contamination in amino acid, in purified amino acids?

DR. FELDMAN: We don't know which is one of the reasons for having this as a topic for the Advisory

Committee. Amino acids that are used as active drug substance are very well identified and characterized but we are not talking about those. We are talking about all the other amino acids that are used as excipients and reagents that are not made through that method and do not undergo FDA scrutiny if you will through a master file which is why we wanted this information and these data presented before you and before us.

DR. DE ARMOND: Usually reagents we get from Cigma(?) or anyone else tells us the percent of contaminants. What is the percent of contaminant of a protein in an amino acid, a pure amino acid or slurry of amino acid preparation; are there actual peptides or proteins there and your acid hydrolysis system, does it break down even proteins such a prion protein to a single amino acid?

DR. BOLTON: I think the purpose of the following presentations is to clarify those issues as much as possible. So, I think Susan, if you have a question that is not related to that --

DR. LEITMAN: I just have a clarification. There is no restriction on use of CNS tissue or MRN in the production of amino acids? I don't understand what the source or what part of the cow they come from.

DR. FELDMAN: Hopefully we will learn that as well

in the next couple of presentations. Anecdotal evidence or anecdotal data provided to the FDA suggests that tissue sources could be bone, fat, hide, hair, those types of tissues but that was anecdotal and this was information provided to us by other companies who got it from their suppliers who got it from the manufacturers but we have no firm data suggesting one tissue over another.

DR. BOLTON: So, I guess for my edification there is a difference here between what is used by the industry and what is permitted to be used by FDA, and so I guess the question is if you are looking at, well, the first issue is are bovine tissues or other ruminant tissues of any sort allowed to be used from countries where BSE has occurred and two, for any animal are there any restricted tissues vis-a-vis bovine, sheep, whatever say, sourced outside of BSE countries?

DR. FELDMAN: That is correct and I would, also, go so far as to say that there --

DR. BOLTON: That was a question. It can't be correct. It was a question.

DR. FELDMAN: And you want a yes or no answer?

DR. BOLTON: Yes, I would like some sort of an answer. Are there restrictions for sourcing bovine tissues for hydrolysis to amino acids in countries where BSE has occurred?

DR. FELDMAN: As of right now I don't believe so, not for amino acids used as anything except for active drug substance.

DR. BOLTON: Okay, and are there restrictions on CNS tissues from animals sourced anywhere?

DR. FELDMAN: I don't know of any.

DR. BOLTON: Okay, so that establishes the playing field on which we are operating.

DR. FERGUSON: May I just clarify one point and perhaps I am misunderstanding your question but if I understand your question you are asking are there restrictions in place in BSE-affected countries on what tissues might be used and I think in Europe the answer to that question would probably have to be yes, that tissues defined as specified risk materials are mandated to be incinerated. They cannot be used for food, feed, drug, whatever. They go right to the incinerator.

DR. FELDMAN: So, that would apply to your other tissue but not to hide or fat or bone?

DR. FERGUSON: Correct. That wouldn't apply to those tissues defined as specified risk materials which is essentially the CNS tissue, intestines, spleen, depending on the definition you use.

DR. BOLTON: Okay, so if I can summarize I think what we might have here are tissues of any type in say the

US that might be hydrolyzed to produce amino acids and non-CNS tissues, non-risk tissues that might be obtained in EU for example and hydrolyzed to amino acids that then could be imported into this country and used as either excipients or reagents. Is that correct?

DR. FELDMAN: That is correct.

DR. BOLTON: Okay, so now we know what we are thinking about in terms of the overall risk and the products. Yes, Ray?

DR. ROOS: Your question was are there restrictions at present for amino acids that would be bovine derived from BSE countries, and the answer I think was no at present. That was your question, and that was the answer?

DR. BOLTON: Yes, the tissue in a country in which BSE has occurred, could tissue be obtained there, hydrolyzed to amino acids and imported into this country, and I think the answer is yes, but not from high-risk tissue.

DR. ROOS: So, I think this touches on the whole vaccine issue again, and whether in fact the guidelines that were suggested with respect to the use of amino acids from bovine products of BSE countries, whether that was a restriction, and maybe we could come back to that.

DR. EGAN: There is probably a lot of uncertainty here, but I think the guidance that has gone out from CBER and from FDA is that bovine-derived materials from BSE

countries not be used in the production of products regulated by FDA by CBER, and that would include or should include amino acids.

I guess we run into some of the problems, and again, if I can come back to the vaccines what do you do about some products where those amino acids had been used, for example, where it is uncertain what the source was, if it had been produced, used in say culture for a cell bank or for you know, viral or bacterial seed, either the master seed or the working seed or what to do with products, let us say that were made using the bovine material, amino acids from a European country before that country was put on the list, what to do with those materials and I guess we, also, need to consider the issue of amino acids per se, even if they were to come from, you know, from a European source, from Europe, do they need to be excluded. I mean there has been an exclusion for tallow derivatives. That exists. Are amino acids more or less of a risk than that?

DR. BOLTON: I think my recollection is that the issue of the cell stocks was dealt with at a previous meeting and that the master cell lines, the master cell banks were to be excluded or accepted as is. Working cell lines would then be produced under these restrictive conditions going forward.

I believe that the existing lots of vaccine were,

also, accepted as is and were not to be recalled, but future lots would be derived under the more restrictive conditions. Is that correct?

DR. EGAN: That is absolutely correct, but at the time that that was being discussed we were not taking into consideration a number of small molecules like amino acids or tallow derivatives.

DR. BOLTON: One more question and then I think we should move to the presentations.

DR. DE ARMOND: I guess perhaps it will be answered in a while, but you showed us the names of four companies that produce amino acids. How many companies are there that actually do this and where do most of the amino acids that are used by pharmaceutical companies in the United States get them? Are they European companies, Japanese companies or US companies?

DR. FELDMAN: It was actually a rather fun exercise tracking down these four companies. We first contacted quite a few of the drug manufacturers to determine their sources of amino acids from which we received a combined list of maybe 17 to 25 suppliers, quote, unquote, and from this list I contacted or we contacted probably 85, 90 percent of them and what we found was that there are probably two or three major companies that make amino acids and a lot of smaller companies.

The four major companies that we could identify were the ones listed there, Ajinomoto, Diechi(?) Degussa and Kirohako(?). We contacted or tried to contact all four of them to get information from them. I received no responses from one of the companies probably because it was in Japan and I might have had the wrong e-mail or phone number. The other three companies were contacted and invited to present. One company stated that since none of their amino acids come from bovine sources it is a moot point and declined the invitation and the other two companies are presenting here, and hopefully they will provide you with some information regarding the scope of their production and how much of a market slice of the pie they have.

DR. BOLTON: With that in mind let us move on to the first informational presentation, and that is Degussa-Rexim's amino acid production process presented by Mr. Gerard Richet, from Degussa-Rexim.

MR. RICHET: Yes, thank you for this invitation to present the process which we are using at Rexim-Degussa for the manufacture of amino acids.

On the first slide you see two names, Degussa and Rexim. Degussa is a big chemical company with several 10,000 people employees and has six divisions and one of these six divisions is Fine Chemicals. At Rexim we don't define chemicals and has approximately 600 employees in total

working on amino acid production now.

We have Degussa since 20 years, but we produce amino acids since 35 years. We have now three plants making amino acids for us.

The main plant is in France in Ham which is between Paris and Brussels with 450 employees.

The second plant is in the South of Germany and the third plant is very recent. This is since the first of September; this is in the South of China in Nanning.

The rest is just to mention amino acids which are produced by other divisions of Degussa for animal nutrition. So, there are plants for DL-methionine in the United States in Belgium, in Germany. There are plants for lysine also in the United States and in Slovakia and one plant in Slovakia for L-threonine.

Now, we come to the processes. So, in Ham we produce amino acids using two processes. The first one is extraction from protein hydrolyzates and second is purification from lower grades produced by other technologies.

In Germany there is one amino acid which is produced by enzymatic resolution of a compound made by organic synthesis.

In China there are four amino acids at the moment produced by biocatalysis and fermentation.

I will now come in detail to each of these processes to explain to you how it works. I have eight slides for the process. The first one tells you which amino acids are produced from hydrolysates, serine, threonine, proline, hydroxyproline, alanine, valine, isoleucine, leucine, phenylalanine, histidine and arginine. These six amino acids are, also, present in protein hydrolysates but for economical reasons it is more often convenient to use ultrafiltration from feed materials.

This slide shows the different steps which are necessary to extract one amino acid from protein hydrolysates. This is a list of steps. After that I will come in detail to each step.

So, there is a selection of the protein, so acidic hydrolysis, filtration, ion exchange chromatography, charcoal treatment, ultrafiltration, crystallization and ultrasterilization.

Now, we come to the proteins. The proteins we use are keratins from feathers, mainly chicken and gelatin from pigs. So, there is no ruminant material. The other chemicals which are used to extract amino acids from protein hydrolysates are acid in base and alcohols and the selection of the material is made using regular audits.

We are audited by the customers. We are inspected by the FDA and we apply the same system. So, we audit our

supplier.

With these proteins the first step is to destroy the protein and we choose conditions which provoke the disappearance of the peptidic balance. Only short peptides remain, short peptides with two to four units and this is obtained by using a large excess of hydrochloric acid, 20 percent concentrated, by heating over 100 degrees, at 105 degrees for feathers and 140 degrees for keratin.

The short peptides, so after hydrolysis we can say that we mean that we obtain 95 percent of amino acids, 4 percent of dipeptides, 1 percent of three peptides.

When we have the protein hydrolysates that is a complex mixture of 15 amino acids we separate the amino acids by ion exchange chromatography. So, it is not so simple as on an antical(?) scale. So, we need several chromatographic steps to get a complete separation. The separation is not only based on ionic properties but also on differences in size the size of amino acids and on the hydrophobicity. So, we see at the same time the separation of amino acids from peptides.

The solutions which comes from the chromatography are these solutions, and they are generally yellow, contain some contaminants which are coloring substances and the elimination of these impurities is made by absorption with active charcoal. It is based on surface adsorption. So, the

active charcoal which is a powder, also, fixes big molecules like all the toxins I mentioned and the toxins because in the past charcoal was the only way to remove endotoxins.

Next step is ultrafiltration. The main purpose is biological purification for removal of endotoxins, toxins which are produced by microorganisms and microorganisms as well. It is due to the fact that the main market of these amino acids is clinical nutrition and especially parenteral nutrition.

We use now membranes with cut off of 5000 to 10,000 daltons and we measure efficiencies of the membrane filtration by making a limulus test. Only after ultrafiltration is done we can go to crystallization.

The biological safety of amino acids is a concern for us since, well, 10 years now and already in 1992 we have been in contact with the Pasteur Institute to evaluate our process and we have started with expert reports and have, also, viral safety report made in 1998, also, made by the Pasteur Institute using two kinds of resistant and highly resistant virus. We have proved with the Pasteur Institute that our process especially in the first step which is the acidic treatment with hydrochloric acid will remove all virus. These amino acids are not produced from protein hydrolysates. So, we buy, in this case, these are generally cheap amino acids with one to three dollars per kilo and we

buy these chemical grade amino acids and make the purifications using similar technologies and each time activated charcoal treatment and ultrafiltration.

Aspartic vistoli(?) of the amino acids before the purification. So, it is for aspartic acid, the bioconversion of phenolic acid. I will come later on to the process. Glutamine and lysine are produced by micrograde(?) fermentation and glycine has no optical center and it can be produced by organic synthesis. In Germany we have one amino acid that we cannot get from protein hydrolysates and it is produced by enzymatic resolution. There methionine is a large-scale product for animal nutrition. Several hundred thousand tons per year are produced in the world. There is an acetylation, then reaction with an enzyme which is produced by malts(?). The enzymes cut selectively one isomer of the acetyl DL-methionine and you get two compounds which are easy to separate by ion exchange, and you get by this way L-methionine. The N-acetyl-D-methionine is rosamized(?) and recycled in the process.

In China we have in development four amino acids. So, China that is since the first of September of this year. The first one is aspartic acid. It is obtained by bioconversion of this simple acid, an acid from the, I would say petrochemical industry, ammonia plus these enzymes. So, after the bioconversion there is removal of the

biocomponents, then precipitation because this particle has a low solubility in water, filtration and drying. The difference between aspartic acid and L-alanine is a carboxylic function. So, this aspartic acid can be submitted to seven enzymatic reactions which remove the carbon dioxide and the beta position to get L-alanine. The rest of the process is similar to the aspartic acid. After the bioreactions you filtrate the polymers, precipitate them in acid, filtrate and dry and two amino acids are produced in China, valine and isoleucine but these are animal-free processes. These are made by fermentation using sugar, cornsteep, ammonia for the protamine ingredients. After the fermentation is finished, biomass is removed. Ion exchange is used to make the purification and again we have the crystallization, filtration and drying.

The same is true for isoleucine. Okay, this is the process that Rexim-Degussa is using for producing amino acids. We are convinced that by all controls that we have on the processes all steps we use, our amino acids are safe.

DR. BOLTON: Thank you, Mr. Richet.

Questions from the Committee?

I will ask the question I asked last time. In your final product what percent contaminants are there and what are they?

MR. RICHET; The amino acids are all in the

Pharmacopeia. So, the basis of the control of the chemical control and biological control of the amino acids established in monographs of the Pharmacopeia in Japan, in Europe or in United States where we satisfy the three Pharmacopeias. The Pharmacopeia uses I would say sometimes third methods and there is the influence of our customers and of our FDA inspectors. We have installed since 5 to 10 years now an additional control which is generally HPLC and here the move is you have to identify if any impurities which have a response of more than 0.1 percent.

DR. DE ARMOND: Let me ask it a different way? Are there any peptides larger than 4 amino acids in length?

MR. RICHET: We have checked the protein hydrolysates with gel chromatography by injecting some molecules with low molecular weight and it was not possible to detect compounds bigger than let us say 1000 in molecular weight.

DR. DE ARMOND: The other question that kind of goes with this is that at no time in any of these processes even in China are the starting reagents the, for instance, of fumaric acid or anything else, are they derived at any point from bovine? None of your starting reagents or your enzymes, do they come, under any circumstance do they come from bovine?

MR. RICHET: The answer that I made for amino acid

is which is produced by cultivating molds and that is same for other bacteria and other enzymes like aspartase or aspartic decarboxylase, those are the processes which are classified as bio, so, bioconversion of fermentations are bovine free. The medium which is used in the future to make the growth of the bacteria contains only products coming from corn or sugar or ammonia, products like that.

DR. BOLTON: Does that, also, apply to the lower grade amino acids which are the source material for glycine and lysine?

MR. RICHET: Glycine is made completely by synthesis. You can have, for instance, you can treat with ammonia, chloracetic acid and you get glycine. So, you don't need any bovine material. Using hedocurate(?) is produced by fermentations and to my knowledge there is absolutely no bovine material in the fermentations and probably the next speaker can confirm that because they produce these amino acids. To my knowledge there is no bovine material in the fermentation.

DR. BOLTON: Perhaps I was confused by the title of your slide. I am looking at the handout. The title of the slide is purification from lower-grade (feed) and then it gives these examples. Are those amino acids not further refined from feed-grade amino acids that are obtained by another source or am I confused?

Your slide, purification from lower-grade feed, it is on Page 4 at the bottom of the handout. I am not sure which slide. It is right after slide 8 of 8 of the, yes, that is right, it must be slide No. 12 or slide No. 9. Three more, continue. Next slide?

This slide. The title seems to imply that these amino acids are purified from lower-grade amino acids that are feed grade amino acids.

MR. RICHET: Lower grade is an evidence. So amino acids which are produced for animal nutrition can have a purity of 98 and 99 percent. For pharmaceutical grade you need at least 99.5. So, from lower grade only means purity between the two, between the starting material and the purified material.

DR. BOLTON: So, those lower-grade source materials for the fine grade are actually produced by your own plants and also do not contain any bovine materials. Is that correct or are they sourced from some other supplier that manufactures these lower-grade amino acids.

MR. RICHET: What I have said is valid for nutrition grade material and lower-grade material. We mix animal feed with non-pharmaceutical grade. So, it isn't the case or animal feed is not used directly. It is converted by organic synthesis to another medium for other applications, but for the animo acids which are used largely to humans so

that what I have said is true that always we have limited material now.

DR. BOLTON: Other questions?

DR. DE ARMOND: Let me say that it must mean purification to lower grade rather than from because I had the same problem which is why I asked the general question. They are purifying this to 95 percent purity for use in feeds. Is that --

MR. RICHET: Yes, lower-grade feed, that is 98 and 99 percent.

DR. DE ARMOND: And that means then that is how that lower-grade amino acid is produced. This slide illustrates how the lower-grade amino acids are produced.

MR. RICHET: Examples of lower-grade amino acid aspartic acid obtained by bioconversion with fumaric acid, you first get a chemical grade and since it can contain endotoxin, it can contain 0.3 percent femeracaceda(?) and the purifications, the aglycosylations(?) that we use here remove or decrease the initial impurities to the pharmaceutical grade. Lysine that is the same. Lysine you may have in the feed-grade material 0.5 percent of oliamin(?) acid for instance. So, it is a product we add in fermentation, it is not quite like pharmaceutical product. It is a little bit lower. It could contain crosidia(?) salts and this doesn't pass the Pharmacopeia standard. That is why

we use the ultra sterilization to increase the purity and glycine is the same.

DR. BOLTON: I see. I actually misread the bottom of the slide. So, the origins are listed, none of which are from bovine materials. Okay.

Ray and then Pedro?

DR. ROOS: The slide before this mentions that the Pasteur Institute carried on some investigation. Were there actually experiments done or did they just review the process here?

MR. RICHET: We sent to them a total description of the process and the study which was made in 1998, so they have had two viruses to the protein before acidic hydrolysis and then they heat to simulate in their lab our process and then they measure the content of virus after the equivalent of the hydrolysis step.

DR. PICCARDO: You start from the assumption that there will be or there are no contaminants. In the very unlikely event, that isn't what you said, but there is a contaminant coming from another source, was any experiment done to, I mean like spiking to see if that procedure destroys BIP or C?

MR. RICHET: Any experiments by adding, well, thions(?) or --

DR. PICCARDO: Yes.

MR. RICHET: This has not been done since we switched, since we use non-ruminant material.

DR. PICCARDO: I understand that, but my point is in the unlikely event that for whatever reason it is a contaminant coming from a source that you cannot identify, in the very unlikely event of a contaminant, my question is if you know for sure that these methods will destroy BIP or C in that event? So, that experiment was not done?

MR. RICHET; No.

DR. BOLTON: Other questions?

Lisa?

DR. FERGUSON: If you would go forward two slides and you are talking about the production at the plant in Germany what is the source of the DL-methionine that you start with there?

MR. RICHET: DL-methionine is produced by organic synthesis. It starts from the beginning from early chemicals like a choline, methinegatapon(?) and this is a total synthesis, only chemical material here.

So, choline is something coming, also, from petroleum industry, not directly the plant.

DR. BOLTON: Other questions?

Very good. Thank you very much.

Our next presentation is by Mr.Mike McLean on Ajinomoto's amino acid production process.

Mr. McLean?

MR. MC LEAN: Good morning or actually I think it is good afternoon, now. I am Mike McLean. I am the quality assurance director for Ajinomoto at our Raleigh, North Carolina facility. This facility makes pharmaceutical grade amino acids for a variety of companies.

I want to give you a little bit of history about Ajinomoto worldwide. The company was started in 1908 using --

Next slide, please?

It started in 1908, by Professor Kukrani Ekada(?), and he isolated glutamic acid as a key flavor ingredient from a component of dosy(?). This is a seaweed, and he discovered that it had the flavoring properties what is now called umami(?). From that time we have expanded into a lot of different areas as a company. Beginning in 1950, the company started doing R&D for fermentation technology to produce amino acids. Before that time it was from an extraction from vegetable proteins, mainly for the food industry.

Beginning in 1960, the company began producing amino acids by fermentation technology in their plants in Japan.

In addition to supplying amino acids to the pharmaceutical industry, amino acids are supplied to foods,

seasonings, cosmetics, sweeteners and animal feeds.

Next slide, please?

For the pharmaceutical industry Ajinomoto is the largest manufacturer. These show some of the other manufacturers. We have around 60 percent. This is a little old slide, 1997, but we have around 60 percent of the world market for pharmaceutical grade amino acids.

So, Ajinomoto feels like we have a responsibility to supply the highest quality amino acids to the world. Most of our amino acids are used as the USD standards and the JP standards.

We have been aware for more than 10 years about the BSE issues and both from the FDA and their letters and information they publish on their web sites, also, from our customers. A tremendous amount of interest has been generated there and, also, from the news media.

We have reviewed all of our pharmaceutical amino acid processes extensively in a science-based approach, and what we did was we looked at the processes to see what type of risk there could be from the process itself what type of risk there could be from the components that were used and then how ready the process was to remove any possible BSE agents.

We believe that the risk of BSE agents in amino acids is extremely remote and essentially negligible for our

production processes. We do not use any ruminant material for our production processes. The extraction processes that we use are all of vegetable origin.

I want to present the Committee very detailed information about our production processes in the next closed session and to help them understand how we have reached the conclusion that our amino acids are safe.

The information I am going to present is from our drug master files which is naturally very confidential and I think it has been mentioned that these drug master files are used by CDER and CBER in review of other drug components and as excipients for a variety of pharmaceutical products.

DR. BOLTON: Before we move then into the closed session, I just would like to ask if there are any representatives of other amino acid manufacturers that would like to make a brief statement before we move into the -- yes, please identify yourself?

MR. BLANE(?): My name is Don Blane. I am representing Kilahago(?) USA. We are one of the producers identified, and as mentioned earlier our production method is fermentation. So, we have discussed with FDA our methods of production and again, similarly we have drug master files in place with the FDA. So the material supplied as excipient or reagent activity adheres to the drug master file which is for the active applications.

DR. BOLTON: Thank you, and I will invite you back at the open public hearing afterwards if you have any additional comments to make.

MR. BLANE: Thank you.

DR. BOLTON: Are there any other representatives of amino acid manufacturers who would like to make a comment at this time?

DR. LURIE: David, unless I am missing something here we have heard from, I assume that the people who are going to speak in the closed session are people who have already spoken here. We seemed to have heard that they don't use any animal ruminant material at all. I am not sure why it is particularly of interest to hear about their processes at all. It seems unnecessary.

DR. BOLTON: Is that a correct understanding? You use absolutely no ruminant source materials at all?

MR. MC LEAN: Yes, that is correct.

DR. LURIE: I suppose then the question would be just to FDA, if FDA is adequately assured by these manufacturers, at least or those who might appear in the closed session that indeed there are no ruminant materials involved in the production of those amino acids.

DR. FELDMAN: The issue I think is not just what the current processes are but what past processes have been since amino acids sit on a shelf for many years or could sit

on a shelf for many years or you can be using amino acid mixtures that were used maybe 5 or 6 or 7 or 10 years ago when you developed your working cell bank or developed the product at that time.

So, we would like to be assured that the processes that were described here are the processes that were used during the height of the epidemic in Europe and in the UK and that if there were ruminant materials used in the past 10 years how the processes have changed since then.

DR. BOLTON: Let me then ask Mr. McLean if your presentation will address only current processes or will it also address historical processes that might have been in place during the years of the height of the BSE epidemic?

MR. MC LEAN: I can explain both.

DR. BOLTON: Okay, then there will be some value in continuing in the closed session.

DR. DE ARMOND: Can't we just ask the general question, have the processes changed in the last couple of years?

MR. MC LEAN: We have one process that has changed. We now use fermentation process for S-serine.

DR. DE ARMOND: Several years ago did anyone use bovine as a source, bovine products of any type as a source or any ruminant product as a source for the final product?

MR. MC LEAN: Aginomoto did not. I cannot speak for

--

DR. DE ARMOND: And we have the others. Did anybody else use that?

DR. BOLTON: The closed session is only going to address their process. Aginomoto has never used any bovine or other ruminant source tissue?

MR. MC LEAN: Similar to what the previous gentleman said, we in the past have purchased pharmaceutical grade amino acids, purified those through our process and sold those as Ajinomoto products. My understanding is that those, in the case of L-serine we have two sources. One of those sources was a bovine-derived source. This was up until 1997..

DR. BOLTON: Okay, I am in a bit of a quandary. So, it may be worth addressing that particular process for the serine that was historically purchased from another supplier as a less pure amino acid.

MR. MC LEAN: Right, and we were purchasing the pharmaceutical grade.

DR. BOLTON: I guess I am confused. if you were purchasing pharmaceutical grade why would you need to repurify it?

MR. MC LEAN: It is a marketing decision. I wouldn't like to --

(Laughter.)

DR. BOLTON: That is beyond me, but I am only a scientist.

MR. MC LEAN: In addition to -- Ajinomoto likes to supply all of the amino acids that any particular company might need, and you know, we are not a boutique shop. We are like a department store. You can get whatever you need, and so we chose at the time to purchase material from competitors, purify that in our process and use that.

DR. BOLTON: What was the time frame for that?

MR. MC LEAN: Up until 1998 for bovine-derived material.

DR. BOLTON: Okay, so, I think it would be worthwhile to consider this. Let us then move to closed session. How do we do that, Bill?

DR. FREAS: At this time I will have to ask all of the members of the public to leave. I am going to ask that you take with you any briefcases, purses, pocketbooks and coats. We want to make sure the room is cleared. Anything left behind we will have to put out in the hall. So, enjoy a nice lunch, and we will reconvene for the public in approximately an hour and one-half. Yes, I would say that at one-thirty we will probably reconvene for the public.

(Thereupon, at 12:10 p.m., a recess was taken until 1:42 p.m., the same day.)

AFTERNOON SESSION 1:42 PM

DR. BOLTON: I would like to begin the open session this afternoon, the open public hearing, if everyone will take their seats. We are missing a few Committee members.

Are there any members of the public in the audience who would like to make a statement, a comment, present information?

Yes, please go to the microphone and introduce yourself.

DR. RADISSON: Thank you, Mr. Chairman. My name is Dr. Scott Radisson. I edit the Journal of Health Communication and have faculty appointments at Yale University School of Medicine, George Washington University School of Medicine and Tufts University School of Medicine.

I edited a book 4 years ago called The Mad Cow Crisis: Health and the Public Good that was published by NYU Press and University College London Press.

I am proud to say that Dr. Les Crawford wrote the first leading chapter in it, and that it is nice to have a successful book that dealt with the science of how we communicate risk.

The reason I wanted to address the Committee today was that I am very concerned about how we continue to look at risk and in particular how a couple of evidenced-based examples of how Committee decisions, both this agency and

other agencies have led to an erosion in public trust and unfortunately led to an erosion of what I am most interested in, the public health, and that is why I can address specifically the three questions that are the charge to the Committee today, but more specifically I am going to actually build on the case study of thimerosal.

As you might know, thimerosal began as a potential risk by an FDA advisory that came out in July 1999, that was subsequently followed up by the Centers for Disease Control's ACIP, Advisory Committee on Immunization Practices, the American Academy of Pediatrics, as well as the US Public Health Service issuing a potential recall of vaccines that would have thimerosal in them.

Just this week in the Wall Street Journal subsequent to an Institute of Medicine that came out this October 1, they were talking about this risk of what has happened to the public health of 1.4 doses of vaccine that ar back ordered now for DTP because of potential risk of thimerosal that never has been supported.

Both the original discussions that were made by and decisions that were made by those three groups, the FDA, the ACIP as well as the AAP were dealing with theoretical risks that were of two unpublished studies, and still the Institute of Medicine highlighted in their report that these were unpublished studies. The report highlighted, however,

that there still if biological plausibility.

What has happened as I have seen from a macro approach over the years that I have been looking at how we look at risk is we continue to lower the bar. We have taken the precautionary principle that was used for environmental toxins, and we have started to apply it to health.

Now, the Institute of Medicine has been charged to look at biological plausibility, and this Committee is being asked to look at the likelihood of transmission.

Last year when this Committee looked at vaccines and bovine source materials there were some excellent quantitative analyses that placed the risk somewhere at 1 in 5 billion. That would be one person on the planet if they would be exposed and if we were so lucky to inoculate everybody on this planet which we know we have not been so successful in our careers.

So, my point here today is that how we determine what risk is which is in each of these three questions, and we don't just look at risk in terms of the theoretical transmission at the molecular level in all due respect to many of you that are involved in molecular biology which is obviously so important, but we redefine risk due to what the Institute of Medicine has suggested as well as other groups continue to suggest to look at societal risks and if we make decisions based upon some of these hypothetical natures that

are out there, and we continue to lower the bar to talk about biological plausibility and theoretical pieces that are made perhaps for academic institutions and play with it in the public health, and I say with it in the public health sector because there have been deaths due to the thimerosal decision. A baby died in Michigan because there has been a 67 percent decrease in hospitals that are immunizing for hepatitis because of that potential theoretical negligible hypothetical risk that has been quoted through different scientific committees.

I was at the CDC as part of the American Public Health Association meeting in Atlanta on Monday and spoke to the Hepatitis Branch and they are having an incredibly difficult time to rebuild the trust at the public level in getting hepatitis vaccines and at the policy level at hospitals throughout the country because now people are questioning what this risk means. Consumer groups are grabbing onto these hypothetical non-peer reviewed scientifically advanced studies that unfortunately are not taken into the public health side of the equation.

So, at the end of the day I hope all of you when you do look at the numbers here and do look at the probabilities and do think of what this means that we don't just think what it means for this Committee, but we think of the cascading effect of what this means for society and we,

also, think of a cascading effect that sometimes doing the right thing is difficult and doing the right thing is not always the right thing to do in terms of always trying to press policy down to a hypothetical infinitesimal risk that is very difficult to translate to the public.

I appreciate the opportunity here. I know this is a charge that perhaps is broader than what the Committee is looking at today. Maybe in the future we will be able to determine what is a valid standard; what are the objective criteria that we need to do and we need to apply in thinking in risk?

It has been 5 years since the mad cow crisis broke out from the original CIAT(?) Committee in the UK March 20, 1996.

Some people predicted it was the AIDS epidemic that Britain never had. Even last year the Frankfort Aldemanya(?) said, "This was the black death reminiscent of the plague of the Middle Ages in terms of what would happen to the continent." We know neither of those has been true. There have only been one hundred and some odd cases now of CJD and today's issue of Science is actually going to say that they are above the hump. The epidemic is definitely going down both with vCJD as well with BSE. This is another from one of the London School studies. We know that science is incremental. We know that ways to validate risk and to

measure risk are difficult at best.

My suggestion again is that we try to think of the societal risk and we try to bring that to a larger proportion in all of our activities whether it be FDA, other advisory committees or whether the ethical nature of what we do, if we are sitting behind the bench and practicing our science on a day-to-day basis.

Thank you very much, Mr. Chairman and the Committee, and I would always be happy to talk in the future about any of these items. My role and goal is to have effective and ethical health communication, and that is what I have been dedicating my life to.

Thank you.

DR. FREAS: For the record I would like to ask this speaker and all future speakers who want to address us in open public hearing to address any interests that they may have on any statements that they have regarding any products, firms or issues that they have for the record.

Thank you.

DR. RADISSON: Sure, for the record I actively consult with a variety of different pharmaceutical companies, public relations firms, academic institutions and my principal position is to work on the communications strategy for the US Government for the US Agency for International Development's public health, population,

nutrition, HIV activities. Those would be my conflicts, and two other conflicts I guess I could say. My wife is Belgian and I, like many of us, I own mutual funds in the health care field.

Thank you.

DR. BOLTON: Thank you. Additional comments or presentations from the public?

DR. LURIE: Could I just comment on that? I have got to say that there is something about that presentation that really seems almost offensive to me as a member of this Committee. The fact of the matter is that there are times in public health where the only kinds of decisions that are available, the only basis for decisions that is available to us is in fact biological plausibility, and indeed that is what we have dealt with in this Committee to a large extent, I think rather well, and I bet that there are people in Britain who wish they had relied on that argument a lot stronger back in the late eighties and early nineties. At times that is the only thing one has, and it is appropriate in those cases as I believe the situation here to make decisions on that basis.

DR. BOLTON: Thank you, Peter.

Additional presentations, other presentations from the public?

Going once. Going twice. Seeing none, we will

move on to the Committee discussion and votes. I open up the discussion to the Committee regarding the preparation of amino acids as has been presented.

We will eventually address at least Question 1, I believe Question 1 as presented on the handout, but I am not absolutely certain of that. So, we may bring it up on the overhead as well to confirm the exact wording of this question.

DR. CLIVER: What I heard in this session has been very reassuring. I wonder, obviously the major question turned on whether materials of bovine origin were being used as sources, raw material, for amino acid preparation, and indeed if the molecular weight is small enough or whatever results, I cannot even get too worked up, if it was of bovine origin. Having said that, we heard from two very large-scale producers that represent a majority of the market. If we are still concerned about bovine origin and so on, why then to what degree can we generalize from what we have heard?

Are there major smaller segments of the market represented by people who are out there using cow brains to make amino acids from? I think it most unlikely, but all the same, if we are going to have a vanishingly small probability of error on this, where will we get that information?

DR. BOLTON: I don't have an answer to that question. Does anybody else want to attempt that?

No? Well, as I read this question there are two words that I think either make this very easy or very difficult to answer, and those words are "can minimize."

Let me just read the question? Does the Committee think that the current manufacturing process and control methods utilized by the manufacturers of amino acids can minimize the risk to allow bovine-derived amino acids from BSE countries to be used as reagents and excipients for the production of pharmaceutical products?

How doe we define minimize, and of course, I would guess that the manufacturing process can do it? The question is does it do it and is it prudent, then should it do it under the optimal conditions; should we then allow companies to use bovine-derived or bovine source materials to derive amino acids from BSE countries? That may be the more cogent question.

Would anyone like to address that?

DR. EWENSTEIN: It just seems sort of easy to me. I mean I think in this case we don't need to worry about major hits on supply because we already know that for most of the supply the question is moot and it seems to me that if anyone really absolutely needs to use ruminant source material they should be required to do a validation

procedure to show that their process which we cannot really evaluate because we didn't hear about the process but we should have as a principle or advise as a principle that a validation step be included so that they can prove that TSE infectivity is destroyed in their process, and it is probably moot anyway but I think that would at least set the bar where it needs to be for the small segment of the manufacturing community that might still be using that material.

DR. BOLTON: That sounds reasonable to me.

Other comments?

Yes, Steve?

DR. DE ARMOND: It, also, seems moot to me because they testified that you don't need to use bovine. What was it, 15 percent of the amino acid extraction was from bovine gelatin and now they are using porcine gelatin. So, I don't like this because they have already shown us that they don't need to use bovine. Why get involved with it in the first place at this stage in history?

DR. BOLTON: Let me put forward a hypothetical scenario, and that is let us say I am an enterprising business person and I realize that there is a tremendous glut of meat and bone meal on the market because it essentially has no value, and I realize that I might purchase this up for a very low price and hydrolyze it to

make amino acids to sell to pharmaceutical companies. So, now the question becomes, yes, most of the manufacturers are using plant source material or other non-bovine material, but I have a new company, and I want to come out and sell this product. What would we recommend? What would the FDA do about the use of that product in these kinds of products?

DR. DE ARMOND: I would recommend, in fact, require that they go to a country that doesn't have BSE in it, such as the United States and use their cattle, have their own cattle ranches where they can assure that they don't get sick cattle. I know that there are companies involved in the formation of collagen. They keep their own herds so that they eliminate that possibility.

So, this guy should be a cattle rancher, also.

DR. BOLTON: I am glad I stimulated some discussion here. Pierluigi?

DR. GAMBETTI: I agree with one correction though. We don't have any case or we have not had any case of BSE in this country which is not exactly the same thing as saying that we don't have BSE in this country.

So, my feeling would be that as I heard already here that really the recommendation would be not to use any amino acid derived from bovine tissue. It looks to me from the presentation that this would not really seriously impair production. It looks to me that the great majority, I don't

know as we were saying the minor producers, but it looks to me like the major producers are not using bovine material, bovine tissue already. So, it looks like it would not impair production, and this in my opinion would be really the effective way to minimize the danger of the health hazards of this problem.

DR. CLIVER: From an expediency standpoint no one could disagree with what was just said. On the other hand we do hear that we are supposed to be doing science-based regulation in the United States and I submit that if you don't have polypeptides in your amino acid preparation there is no way regardless of the origin for that to be an infectious agent, prion or otherwise.

Now, in part of the things I do in addition to food safety, I work with water and waste water, and there is a lot of recycling of water going on now, and it invokes a lot of public angst, and so, I have a pair of slides that I use, one showing the very precise structure of a water molecule and then a sewage molecule. This is water that has at some time been in the sewer and in the public perception it can't ever be fit to drink again. In fact, we drink a lot of recycled water especially in Los Angeles, but my point is to the extent that we learned what amino acids were when we took our first course in biochemistry, these are not disease agents and to the extent that we can prepare amino

acids in a scientific technologically sound way I think it is an unfortunate perversion of science to decide that because that particular molecule of amino acid at some time was part of a cow that it is no longer fit for any use in human pharmacopeia. That is just my point of view, but I think we get a lot of emotion and science gets kind of elbowed aside by expediency and what is politically correct, and at some point if this is a panel of scientists we have to admit that it is very difficult to tell an amino acid that is of bovine origin from one from bacteria or from plants.

DR. EWENSTEIN: I agree with that, but don't you think that as I was trying to say that you know, it is incumbent upon the manufacturer to do an actual validation and not just to sort of suppose that the hydrolysis step is sufficient?

DR. CLIVER: I have no problem with that at all. What I don't like is the idea that somehow or other because we bovine derived it is never going to be a problem amino acid, but as far as validation of a process is concerned I think anything that they are going to inject in me I would like to have the process validated.

DR. ROOS: It seems to me unwise to, if one uses a bovine product to get it from any BSE country. So, whereas I could see that there may be a reason that somebody might

want to make an amino acid from a cow, I would say that if one does that it should be from a non-BSE country, and it should be validated.

I think that a little similar issue that perhaps this question touches on has to do with products that are on the shelf or that involve the use of a seed stock, and I don't want to exactly go back to a vaccine but probably there are going to be other drugs that might actually have some remnant of bovine amino acid from a BSE country that might be in use today, and it is hard to deal with that at present.

In the case of vaccines I think we explored that issue extensively, and I think we were reassured that there was this enormous dilution and that we were dealing with a safe product. We haven't really identified a comparable issue in other drug products in use in the United States today, but there may be, and perhaps if we identified those that they should be explored.

At the moment it seems like we don't have an issue because we have no ongoing use of bovine-derived products from BSE countries in which amino acids are being actively made at present.

DR. LURIE; I think what Pierluigi is saying is eminently reasonable and I remain concerned, of course that some 20 percent of the worldwide amino acid market was not

represented here, and so, we really don't know what they are doing.

To go to Bruce's point I mean the amount of information that we have about the various purification steps here is nothing like what we have had, for example, last time with gelatin. I mean this was the merest sketch of the purification system. We simply don't know much about it. So, I think that Pierluigi's approach is absolutely a reasonable one here.

My question, assuming we go that route is well, I guess one recommendation would be is to put a letter out to the people who have received some of these bovine-derived amino acids asking them to take it off the shelf. That seems to me a useful thing that the FDA could call upon the manufacturer to do, but I guess my question would be if we go Pierluigi's route what is different; what have we actually done? I mean isn't that what the 1991 letter said in the first place when the FDA wrote the 1993 letter at least? isn't the FDA here asking in effect for an exception from what they did in 1993?

In 1993, there was a letter sent to manufacturers saying, "Do not source materials for administration to humans from BSE countries." Right? So, if we were to endorse what Pierluigi is saying, all we are saying is yes, we agree with the 1993 letters that apparently some of the

manufacturers didn't pay attention to. Is that right?

DR. FELDMAN: I think that is absolutely correct. One option of the Committee is to state that, I mean that is our word, to qualify it as an exception from the 1991 guidance and letters to industry. The Center for Biologics felt that given the existence of this Committee it was not our determination to make that decision but rather yours, if you feel that the evidence presented today supports that decision. So, from a regulatory perspective and from a scientific perspective I, personally, would be very happy to see an exception for amino acids if one is justified.

If not, then we just go back to the 1991, 1993 and 1994 and 1996 and 2000 statements and letters to industry stating that no bovine-derived products from BSE countries are permitted in use of drug products as excipients or reagents with no change essentially.

DR. LEITMAN: Particularly after what we heard this morning I think the definition of a BSE country is a moving target. It doesn't stay stationary. I have heard multiple veterinary scientists say, "Just wait until the first case comes up, is recognized in the US, and all of a sudden the whole world becomes a BSE country."

So, I would let the 2001 restrict source material by country of source. As far as the second issue I think despite the best of QA efforts and well-validated processes

for manufacturer, breaches in good manufacturing practice do occur. They are rare, but they could have devastating consequences. So, since the two major manufacturers have told us it is not necessary, they haven't lost market share by not using bovine source material in their products and perhaps the reason the other manufacturers aren't here is because it is not an issue for them, I don't think it makes any impact to do the very safest thing possible that was suggested which is to restrict use of any bovine material from amino acid production. That would be my take from the discussion so far.

DR. BOLTON: Additional comments? Ermias?

DR. BELAY: I was just going to say that it appears that we have a good system already, and from what they told us they are not using bovine sources. So, why change the system when you don't have any problem right now? So, continue the way they have been doing so far and avoid using bovine tissues as long as it does not affect the supply or have any other adverse effect that we should start to worry about, and from what we heard it doesn't appear that it is any problem at all right now.

DR. LURIE: There are two small problems. One is that at least one manufacturer did not comply with FDA's 1991 letter and did continue to use bovine materials we think from Europe, I think that is correct, despite that.

That is one problem although that seems to be in the past and to the extent those get taken off the shelf that does become a non-problem.

The second problem is there is 20 percent of the market we don't know anything about.

DR. ROOS: Son, one of the issues is should we restrict the preparation of any amino acid so it does use a cow from anywhere, and you know at the moment I mean there are bovine products that are in use from non-BSE countries routinely and if one forbids this with respect to amino acids it seems to me that one is kind of making an exception as far as the general use of bovine products. I think it is a little more consistent to bar amino acids made from bovine products of BSE countries. In the case of tallow where there is an exception it is hard to exclude tallow from other uses we have, and it is a very low risk we think.

In the case of amino acids it looks like there are many other alternative sources. So, I don't see any reason why we should import that bovine product from BSE countries, but I didn't think we should necessarily restrict amino acid preparation from bovine just because there is an alternative source here.

On the other hand I think we can ask for appropriate validation of bovine products. What exactly that appropriate validation is I am not sure at this point but

would touch upon some kinds of options that are appropriate.

DR. BOLTON: Thankfully that is not our task today to define criteria. I think it should be re-emphasized that bovine products, especially fetal bovine serum are used in producing many of these products. So, that is already a given. Those are not sourced from BSE countries though. They are sourced from non-BSE countries. So we wouldn't want to make this I don't believe more restrictive by saying, "No bovine material can be used."

On the other hand it might be prudent given the fact that BSE countries or BSE-free countries may in fact be a moving target to ask that those processes that use bovine materials as a source for amino acids be validated in a way that those using plant or bacterial sources would not be required to do so.

Jeffrey?

DR. MCCULLOUGH: Another reason to take that position is maybe heresy but consistency from this Committee. We have agreed that people can donate blood from non-BSE countries and we agreed that plasma donors are, also, acceptable. So it would seem, while I agree that BSE countries are moving target it would seem inconsistent to allow blood donation that we spent hours agonizing over from non-BSE countries but at the same time restrict source material.

DR. BOLTON: Again, I just want to make a comment. In my opinion the safety of amino acids having gone through the hydrolysis and purification steps, ion exchange, filtration all the things, the likelihood of any prion-infectivity surviving is very, very low. It is so extremely low as to be almost inconceivable. So, we don't want to be arguing over this very, very minimal risk involved. However, it might make sense to say, "Look, the problem is again, how faithfully are the manufacturing steps followed? How likely is there to be a breach?" Those things can be verified by validation studies and by quality assurance programs. Should bovine materials be used from non-BSE countries? It provides at least an extra level of safety or assurance of safety that might be desirable for amino acids produced from bovine source materials as opposed to plant or bacteria sources.

DR. LURIE: I generally but not specifically agree with what you are saying. I don't think that the right analogy here is that we take blood transfusions. I think the right analogy is to other restrictions we have placed on other bovine source materials and in that case I am not aware. and maybe FDA can correct me on this, I don't think there is any other place where we have ever said, "No bovines, period."

It seems kind of ironic to apply that in light of the situations of the world, and that so, I really agree

with Ray on that, but I, also, agree with Bruce that I think if somebody wants to go to a non-BSE country and source their amino acids let us force them to do some validation steps and probably what will happen is that they will decide let us not use bovine.

DR. GAMBETTI: I think there should be at least two elements that we should consider in every recommendation that we make. One is safety, but the other, also is impact that whatever recommendation we make has on the consumer, the user.

So, not necessarily we would be consistent if we recommend different things for different products. For some of the products safety has to be always beef as choice but reduced by the necessity of not limiting the availability of the product. In others like this one it looks like we can be in a sense more restricting even if the product is less dangerous because it doesn't look to me at least that limiting the source of the bovine tissue really impairs availability of the product. So, I think there are these two factors that have to be considered every time we make a recommendation.

DR. DE ARMOND: I think the danger, Pierluigi that I am catching from you a little bit here is that every cow has to be assumed to be potentially sick with BSE, and I don't think that is necessarily true.

I think you can have sequestered herds even probably in Great Britain in which that wouldn't happen in which they are fed soybean pellets instead of any type of meat product of any type and I think in the United States as I say pharmaceutical companies in the United States have sequestered herds that they can get their products from.

I think it is absolutely possible to have prion-free cattle herds certainly under very rigid control and probably in the United States broadly but I think if you could define those, I think they should have the ability to take bovine if they can prove that the animal doesn't have BSE.

So, I find that it shouldn't be a broad spectrum inhibition of the use of all cattle. Now, bovine from a BSE country to me that is the only question that I have to worry about.

DR. GAMBETTI: The problem is always the same, how we define BSE and non-BSE countries, especially a non-BSE country. For me the only definition of a non-BSE country is a country that has done extensive testing and has resulted consistently negative, and I don't know of any such country.

DR. DE ARMOND: But there are herds that are just by themselves in which that has been done.

DR. GAMBETTI: Yes, if they use their own cattle then there is no question that that can be safe.

DR. BELAY: If what Steve is saying can be done, and I don't have any problem with that, but at the same time I believe we have to be very careful not to say to the companies that they have done wrong by switching voluntarily from bovine sources to other sources. In other words they are voluntarily sourcing their animals from other than bovine origin. Our general statement should recognize the fact that the company has taken measures and we should commend them for that.

DR. LURIE; I disagree with that. They have done something wrong. In 1991, the FDA asked them not to do it, and at least one company did. They did do something wrong.

DR. BELAY: I am talking about the current practice.

DR. LEITMAN; A quick comment. This Committee in considering blood donations pushed the restrictions to the limit to which it felt the blood donation and collection organizations could tolerate the restrictions. So, if you follow that analogy to push amino acid source material to the limit to which their industries could tolerate it, it would be to push it to completely exclude ruminant animals. So, there is an analogy there. I don't know if I would follow that analogy, but that would be a proper analogy.

DR. BOLTON: I guess I feel that we must be careful not to send the wrong message and that message would

be that there is something wrong with cattle from non-BSE countries. Otherwise why would we exclude using that as source material to derive amino acids which are in the very process themselves essentially safe? So, I am very, very concerned that we would go too far. I mean basically the FDA is asking us for advice on whether we would reduce the restriction and allow bovine source material from BSE countries to be hydrolyzed and used as amino acids.

It seems clear that the Committee is not comfortable with that idea. However I don't think that we should move farther in the other direction to say that we don't want any bovine material at all used in this. I think clearly that sends in my opinion the wrong message.

DR. ROOS: I think under some circumstances I might accept amino acids that are bovine derived from BSE countries perhaps. In other words, going back to the vaccine issue although, and those are complicated ones, and I don't know whether we want to go into that, but we are dealing with big dilution factors and a very safe product are far as partitioning and hydrolysis, and that makes the question a little bit more complicated here because what are those products and what is the dilution and can there be an alternative source and we really haven't addressed that here, but it is good to remind ourselves in a way we have made a little bit of an exception there as far as letting

those products that might have some contamination in animals today. It would be great to in fact be able to replace those materials if possible with safer ones if possible.

DR. BOLTON: But would you be suggesting that products that may have contained amino acids from bovine sources from BSE countries be pulled from the shelves and destroyed? My personal feeling on that is that the products that are out there now are safe. It does not make sense, in fact, is probably counter productive to ask for recalls and destruction of products in those conditions.

It makes sense to me to move forward and look at this as a change in policy from this day forward in terms of amino acids sourced from either bovine or ruminant sources in BSE countries. That is about as far as I would believe would be worth going.

DR. ROOS: But my guess is that ones are still being put on the shelf like that, for example, vaccines might continue to have these diluted amino acids. I believe that --

DR. BOLTON: From the original cell banks.

DR. ROOS: Right, and maybe we should get off the vaccine issue but there may be other comparable drugs that might contain products that have amino acids from these BSE countries that continue to be put on shelves.

DR. BOLTON: That is a question that perhaps

somebody from FDA could answer whether there would be products that would fall into category.

In the meantime, Sue, you have a comment?

DR. PRIOLA: All of this discussion seems to get a the first half of this question and that is do we think the methods used to manufacture minimize the risk of allowing BSE contamination. I haven't heard anybody disagree I think with that assessment given the way these processes are used. So, long shelf life might actually be not much of an issue if you think to start that the risk is minimal that anything could get through those manufacturing processes.

That would be my response to that and the second part to this question which has to do with deriving amino acids from cattle from BSE source countries the consistent thing to do would be to, I think, just keep that prohibition in place because that is the prohibition that this Committee and the FDA has put into place for everything else. Just don't use BSE source materials.

The fact that it is a moving target is completely correct, but it is a moving target, but since industry isn't using those materials anyway the target can move all it wants. It doesn't affect anything if industry continues to pursue it the way we have been told.

DR. FELDMAN: To answer the question that was raised regarding other products besides vaccines at the

Center for Biologics all therapeutic proteins are made from recombinant DNA technology and most therapies are made using culture methods which imply culturing amino acid broths of one sort or another. Maybe anything developed in the last year would not have any questionable sources of amino acids but certainly anything made in the last 10 or 15 years would and anything that was banked during that time frame would have sources of amino acids possibly unidentifiable at this point. That is certainly questionable.

So, we are talking about hundreds and hundreds of products potentially.

DR. BOLTON: But still those are, the concern is that those are either excipients or more likely reagents in the production of the product which are then really mostly removed from the final product.

DR. FELDMAN: Actually I wouldn't even say that those could be considered as excipients because if it was an excipient it would have gone in the final product which would have had a shelf life of at the most maybe 2 years. So, we are talking about reagents at this point used in the production of the final product.

DR. BOLTON: It is a minimal risk on top of a microscopic risk of something that is sitting on the shelf for the last 2 or 3 years.

DR. FELDMAN: I think it is freezer for the last -

DR. BOLTON: I think we have to be careful not to get carried away with these extremely low levels of risk.

DR. CLIVER: I am okay with what I just heard but of course there is a good deal of the consumer advocacy public out there that would be very upset about the recombinant DNA used in the production. This is a can't win situation. I do not subscribe to the I think all-too-prevalent notion that public health is best served by maintaining an adversarial relationship between industry and regulatory agencies. My feeling is this is a partnership and in the present instance we have seen that depending on how you interpret the advisories from earlier industry has taken voluntarily a course that we now say is very reassuring.

Now, we can turn around and tell FDA that whatever industry is already doing you are supposed to say now has regulatory status. Don't change. You have got to keep doing it but that is kind of saying that in totalitarian society everything that isn't prohibited is mandatory.

We are in a situation where industry has done very well without regulatory pressure and I am not saying that we cannot advise FDA to institutionalize that, but I think we should recognize that industry has in its enlightened self-interest a considerable stake in the public health, and they

have made some moves that are laudable, and rather than saying, "Do you still beat your wife?" I think we should be saying, "Yes, they can. They did, and maybe we don't need yet another regulation."

DR. EWENSTEIN: I think we are sort of beating on one point here, but I think the point that was just raised by the agency is one that we haven't really addressed, and that is if there is material that came from the ruminant source and got into the manufacturing process 5 years ago, 3 years ago, even last year from one of the 20 percent of the manufacturers that we don't get to hear from, what do we think about the risk there, and I guess since we don't know anything about the manufacturing process we can only extrapolate from the processes that we heard.

So, I think what they are asking for is some sort of guidance in that situation. I think we all sort of see which way, you know, things are moving and the manufacturers are already moving in that direction for a variety of reasons, but I think it is this sort of look back question that is sort of implied in two and three and four which we were told we could answer or not at our discretion, and I would like to hear us discuss that.

I feel like from what I know about the biochemistry of PRP scrapie or TSE infectivity these processes that we heard were pretty robust, and the risk I

would agree with you must be pretty small, but I think we should make sure we have a consensus on that because I did hear some other experts on the Committee talk about the risk of hydrolyzed peptides and maybe we need to sort of think about that question more precisely.

DR. DE ARMOND: Is there the equivalent of an Underwriter's Laboratory who independently looks at products and assays them for proteins and for purity or is this all done basically by the company?

DR. BOLTON: My understanding is this is all done by the companies to validate and quality control their products. I kind of doubt that there is anybody that would have the money and the incentive to do that.

We have done many amino acid analyses of PRP over the years. I hate to say that we have never taken the hydrolysate and injected it into an animal to see if there was any residual infectivity. I think the problem always comes back to these hydrolysis procedures are not perfect. They certainly, the whole intent is to harvest as much in terms of individual amino acids from protein as you can but still there are small peptides that probably survive.

The likelihood of any significant amount of infectivity surviving just the initial hydrolysis procedure is extremely low. Bob, I don't know if you as an independent person wanted to comment on that, but it seems very unlikely

to me that this would survive.

PARTICIPANT: For one thing you are working at over 100 degrees. So, it is hot, and 100 degrees in just plain water is not totally effective but it does have some reducing effect but you are in hydrochloric acid, and I didn't catch what the normality is, but my guess is it must be around one or better.

DR. BOLTON: No, it is six --

PARTICIPANT: It is really hard for me to believe that there is much survival. I would think that the danger would be not so much in the process but in cross contamination and whether the process is secure in that regard or not could be an issue.

Both David Taylor and I have talked about the problem of material escaping even Autoclave temperatures by virtue of drying on surfaces and I think that could be an issue here, too, you know if you have got something that doesn't actually get exposed in hydrolytic conditions; you could have some infectivity escaping through but again you are taking it through a purification process and the actual mass contribution must be extremely small, and so it would have to be at a very low level.

DR. MC CULLOUGH: There is another minuscule part of a minute problem that I would like just to call to the Committee's attention but let me say that I do not propose

doing anything about this, and Drs. Stroncek and Leitman might want to comment or disagree with me, that is the kinds of novel cellular therapy products that are generated these days for patient treatment such as manipulation of bone marrow for transplantation, activation of peripheral blood lymphocytes and others where we are creating novel cellular therapy products for patients and then to the issue of material that would have been produced over the years that may still be out there. I mean we have bone marrow and cellular products in our freezer that were collected 10 and 12 years ago, and so some of this material, some of these were even processed with bovine serum albumin and material that isn't even indicated for human use.

So, it is possible that there are cellular products in storage that will be used in patients that were processed with some of these kinds of materials. I think this is again such a minute issue I am not proposing that any change be implemented to deal with this.

Also, it may not be practical because these materials are usually very uniquely prepared for a particular patient, and so it would not be medically justifiable to discard something that is the only product that you might use to treat a patient when the time comes.

DR. STRONCEK: Somewhat I think I agree both with what Dr. Leitman and Dr. McCullough have been saying. The

risk of amino acids is really very small, but the potential harm if we are wrong is much worse than with blood products because you know liquid blood products have a reasonable shelf life. They are not around much more than a year and yes, there is a problem with the plasma derivatives if something were contaminated because they do hang around but we track them pretty well, but with amino acids all the culture media we use for all cellular products, you know, we are making peptides for vaccines. So, it is conceivable if cell lines, you know, if this were a problem with these amino acids we would have cell lines and patient material infected for years. Everything would be infected.

DR. BOLTON: Again, I would just like to remind everybody that infecting cell lines with prions is not an easy task and it is not something that is likely to stay around for very long unintentionally.

Suzette?

DR. PRIOLA: I would just like to make comment. I think it gets back to what Bruce mentioned and that is there is not an awful lot but there is data available that shows that infectivity in the prion diseases is associated with larger sized aggregates of PRP and that the soluble, the normal form of PRP which is about 25,000 daltons is not that I know infectious no matter how you get it, even if you try to separate it from the PRPSC fraction. It is not

infectious. So, the size cutoffs that were described to us in these manufacturing processes are way below that 25,000 daltons.

As to the issue of peptides I don't know of any instance outside of one transgenic mouse model where a PRP peptide has ever been shown to be infectious. So, that to me points to excluding even 6000 and 1000 molecular weight peptides.

DR. LEITMAN: We have heard a lot of very good discussion. Maybe we could return to Question 1, and the first slide says, "Current manufacturing processes and control methods." The current methods we heard described to us by the two major manufacturers are what the FDA is asking us to consider I think in Question No. 1.

Are we ready for a vote?

DR. BOLTON: I am not sure because the current manufacturing process doesn't involve any bovine material. So, I mean the source material used is not bovine. The manufacturing process, I guess we could vote on that. I am not sure it makes sense to do that.

My sense is that the Committee is one, not interested in having BSE countries be the source of bovine source material for amino acid production.

My sense is also that we encourage the manufacturers as they have done to shift to non-animal

sources but we have not suggested that that be required and I guess the third thing that I sense is that, and this may be wrong, and you will tell me if I am wrong, that we are not particularly interested in doing recalls on products that may have had bovine source materials for amino acids in the past that are currently on the shelf.

Now, am I right or wrong in this assumption?

DR. LEITMAN: You said, "Non-ruminant." I think we got non-ruminant rather than non-animal.

DR. BOLTON: There was one suggestion at one point of non-animal. No, I would take non-ruminant. That would be fine as well. Again, I think my sense is that that would be encouraged but not something that we would suggest as a requirement.

DR. CLIVER: Ruminant is maybe the half a loaf approach but if we are going to say, "Animal," or even if we are going to say "Ruminant," let us purposefully exclude milk and perhaps some other specific products that are pretty well cleared of suspicion. Clearly you are not going to specifically go to a BSE country to get milk to make whatever bovine product you might want, but all the same this is not a risk material and as such while it is an animal product chicken feathers are another.

If we just generalize we don't want anything from animals in there I think we may catch some stuff from that

net that we don't want.

DR. ROOS: Just adding onto your summary data I think we are urging companies not to use ruminant or animal material as a source for amino acids and if they do it would be from a non-BSE country that we would like some validation with respect to that material.

Second, I guess with respect to the shelf issue what I would say is that I am comfortable at the moment with what I have heard of the purification procedure. My guess is that the materials that we are talking about here that might have amino acids from BSE countries are ones in which there is a lot of dilution and the ones that may be difficult to easily replace in other ways and what I would suggest is if there are particular issues with some of those products that the FDA alert us to those and we could examine them on a more individual basis because I could see potentially that there could be a concern about one or another product but at least at first glance I don't think I am going to lose sleep about this. I think they have a pretty good purification partition. They are starting with material that is probably reasonably safe and they have a huge dilution factor, but if there is something out there that we should know more about and talk about, fine. I think the Committee has a role and could help out.

MR. BLACKWELDER: I am a statistician, and we

haven't been looking at any data or talked about planning any studies today. So, there really hasn't been much for me to talk about and at the same time it seems then that there is, unless there is a very strong reason not to do this that there is no evidence to suggest we should change anything or break new ground, and I think much of what has been said is in that same vein, and I believe your proposals of a few minutes ago pretty much are in that vein. That is a reasonable principle. I would like to suggest whatever recommendation we have.

DR. DE ARMOND: I want to say exactly the same thing. I think we are beating it to death right now, and your summary was perfect, and we can answer this question I believe very accurately.

DR. BOLTON: We are good at beating things to death, and we should do what we are good at, right?

Other discussion?

I am just trying to actually recollect what it was that I said which is not always easy.

DR. LURIA: I agree with that as well, and with all due deference to FDA, can't we just vote on what you proposed? I think that these questions are actually quite complicated. It gets to current manufacturing. It gets to minimize, all these difficult terms. I think you put forward a good summation of what most of us think. Why don't

we endorse that and leave it at that?

DR. BOLTON: We all understand what it was that I said.

DR. EWENSTEIN: I was going to say that I think we need to, you know if this is a yes or no, I think we can have that little addendum there about the what ifs, but if this is a yes or, then I think to be consistent with what the Committee is saying and with what you summarized we would be voting no on this which is to say that we don't want to make an exception for amino acids but that we want the general policy about not sourcing from BSE countries to be in effect for amino acids even though we feel comfortable.

DR. BOLTON: Okay.

DR. EWENSTEIN: And then the other issue is going to come, having all that in our heads, but then No. 2 to try to translate what you said into the answer to No. 2, it would be that under most circumstances we would feel that the risk/benefit ratio would favor continuing to use the products even though they may have come in contact with these ruminant-derived amino acids that they shouldn't have in the last few years. We would not be asking for a recall. So, I think we could get through Questions 1 and 2 with what you said, with what you summarized.

DR. BOLTON: That sounds like an excellent plan.

What I will do then is call for a vote on Question No. 1.

No, you are not going to ruin my perfect plan, are you?

DR. FELDMAN: Only if you want me to. I was going to state that when I gave my presentation I mentioned that I had three questions for the Committee to focus on, but we would certainly accept any revisions or modifications to those questions and what you have proposed is perfectly acceptable to us.

DR. BOLTON: Good, then anarchy rules as usual.

We will vote on the first question and I will try to summarize the other points, and then we can vote on those either individually or together.

The question is does the Committee think that the current manufacturing process and control methods utilized by manufacturers of amino acids can minimize the risk to allow bovine-derived amino acids from BSE countries to be used as reagents and excipients for the production of pharmaceutical products, and now we will take the vote.

Let us do a name vote.

DR. FREAS: We would like to do it by name vote for the record, and we will vote in the order in which we are sitting at the table.

Dr. Roos?

DR. ROOS: No.

DR. FREAS: Dr. Ewenstein?

DR. EWENSTEIN: No.

DR. FREAS: Dr. Piccardo?

DR. PICCARDO: No.

DR. FREAS: Dr. Crawford?

DR. CRAWFORD: No.

DR. FREAS: Dr.Belay?

DR. BELAY: No.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: No.

DR. FREAS: Dr. Nemo?

DR. NEMO: No.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: No.

DR. FREAS: Dr. Blackwelder?

MR. BLACKWELDER: No.

DR. FREAS: Dr. Stroncek?

DR. STRONCEK: No.

DR. FREAS: Dr. Bolton?

DR. BOLTON: No.

DR. FREAS: Dr. Lurie?

DR. LURIE: No.

DR. FREAS: Dr. DeArmond?

DR. DE ARMOND: No.

DR. FREAS: Ms. Walker?

MS. WALKER: No.

DR. FREAS: Dr. Priola?

DR. PRIOLA: No.

DR. FREAS: Dr. McCullough?

DR. MC CULLOUGH: No.

DR. FREAS: Dr. Leitman?

DR.LEITMAN: No.

DR. FREAS: Dr. Cliver?

DR. CLIVER: Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: No.

DR. FREAS: And I would also like to get the industry representative's opinion.

DR. PETTEWAY: No.

DR. FREAS; Okay, so, there should be one yes vote, Dr. Cliver. There should be 18 no votes and no abstentions and the industry had a no opinion.

DR. BOLTON: Okay, very good. So, now, I will try to summarize what I think I was saying, point No. 1 that we would recommend that ruminant source tissue not be used from any BSE country. Does that sound correct? Should we vote on that? Let me package all these things together.

Secondly, we encourage, we recommend that the FDA encourage the use of non-ruminant source material preferably non-animal source material.

Third, the FDA ask for validation of processes to produce amino acids when ruminant tissues are used as a source material for production of amino acids and four that the FDA not recall products currently in, would you say in use or having already been produced where they might have been produced with or contain amino acids that were produced from ruminant source materials, that the FDA ask for validation of processes for production of amino acids where ruminant tissues are the source material or something to that effect.

DR. DE ARMOND: Do you have to specify the validation for PRP scrapie?

DR. BOLTON: Yes, validation for removal of infectious prions or PRP scrapie as a surrogate marker.

DR. GAMBETTI: Mr. Chairman, point of clarification. When you talk about Point 4, I guess, not recalling products you referred to amino acid that had been already purified and ready to be distributed by the manufacturer or, also, to amino acids that are on the shelf and eventually will be used to make the final products. If I understand correctly there are amino acids of ruminant origin on the shelf and those may be used or our recommendation should deal with this kind of product whether we recommend that it would be used for the final product or that one that has not been used yet we stop.

DR. BOLTON: No, my intent and correct me if I am wrong in the sense of the Committee was that products that are already manufactured from amino acids would not be recalled. Amino acids that are unused that were derived from bovine tissues from BSE-affected countries should be removed and destroyed. Does that sound right?

DR. EWENSTEIN: That sounds right. I would just leave the last point off Point 4, because I think that is going to come up when we vote on No. 2.

Oh, we don't have to vote on No. 2? Okay. That is really the answer to No. 2 which was that I guess we would all be voting yes or most of us would be voting yes that there would be certainly circumstances maybe almost all circumstances where the risk/benefit ratio would favor being able to use that product even though suspect amino acids had been used in the manufacture.

DR. BOLTON: Let me turn it around and ask the question is there any member of the Committee who is concerned that there is a product that should not be used given that it may contain amino acids or may have been produced using amino acids that were derived from bovine source tissue from I guess potentially a BSE-affected country?

Even with my glasses on I don't see any. So, there really are not at least products that we can think of at

this time --

DR. EWENSTEIN; No, the only reservation I have, and I think the FDA would be obviously on top of this is that we have heard about two very robust processes. We don't know about all the processes that are used to make amino acids that might have gone into products that are out there, but I think we can rely on the FDA to extrapolate from what we have heard and not go too much beyond that because one could imagine less robust processes might have been used by other companies.

DR. BOLTON: In the interests of saving time why don't we vote on the first three, leave this recall of products part out for now and I think we could move on then, except that I see more hands rising all the time here.

Lisa?

DR. FERGUSON: Two points, and I will try to run through them very quickly. On the first point we are recommending that the product not be sourced from ruminants, I feel like we need a caveat in there somehow for such things as milk proteins, gelatin from hides or from hair. There are certain things out there which have been demonstrated or widely accepted not to present a risk. So, if we can either have that caveat implicit or write that in there, I think we need to do so and I would make just one side comment. My understanding of the casein or the milk

protein I think most of that actually is produced in Europe. So, if that is a component of anything that would primarily be sourced in Europe. Anyway, the second question that I had is actually just a clarification on the third point I believe it is about the validation, and correct me if my understanding is wrong.

What we are saying in Point 1 is don't use ruminant source from a BSE-affected country and Point 2 we are saying, "Try not to encourage or try to encourage non-use of animal proteins anyway," but then Point 3, if you are going to use animal protein which would be from a non-BSE-affected country we are saying validate the process.

DR. BOLTON: Right.

DR. FERGUSON: Okay, my concern there is that we are being inconsistent. We are not asking for validation of a process for anything else where we are sourcing bovine material from a non-BSE affected country, are we?

DR. BOLTON: No.

DR. FERGUSON: So, why would we choose this specific product which I think we are all accepting is a pretty minimal risk anyway to start to make that recommendation?

DR. BOLTON: That is a good point and now things are getting more complicated all the time.

DR. CLIVER: Lisa already took care of the milk

thing I was going to raise but let me say another kind word about feathers. I really think when we talk about animal products that we have to include some exclusions or else we are going to get ourselves into areas where we don't need to be, or have any reason to be.

DR. BOLTON: Good point.

DR. WILLIAMS: Actually those are the two points I was worried about, too, the casein situation and then the situation of broadening things out to be animals. That certainly includes birds.

DR. BELAY: Can you review Item No. 3?

DR. BOLTON: That we would ask the FDA or recommend that they encourage the use of non-ruminant source material now with the exception and I guess I also added and/or even non-animal source material and now we have exceptions for milk, hair, feathers and some other specific items. Does milk, hair and feathers pretty much cover it?

DR. FERGUSON; Hide, gelatin or anything associated with hide or hair.

DR. BOLTON: Is the list now going to get so long that it doesn't make sense to have that recommendation?

DR. FELDMAN: If I may there are a number of points that need to be brought to the attention of the Committee. One, milk, milk-derived proteins or components, hair, feathers, for instance, I believe are already excluded from

the regs and so should not be of issue here under these in this conversation.

Secondly, in terms of validating processes for all bovine-derived products from non-BSE countries, fetal calf serum from the United States and from New Zealand and Australia is the bovine-derived product from non-BSE countries and is used in pretty much everything that the Center for Biologics regulates and there is no way of validating that purification process.

Thirdly, the term "validation" itself needs to be clarified by this Committee if it intends to use it so as to give us some guidance as to what level of validation would be appropriate and if you start going into hide and hair and other components the list is going to get too long and too involved and it would simply be beyond the ability of the agency right now with the resources that it has to start regulating and changing policy and changing products on the basis of those parameters.

Now, I throw it back to you.

MR. BLACKWELDER: I am thinking not on the basis of science but on kind of trying to be logical that especially from the last few things, Dr. Bolton, maybe we should just have the first one of your recommendations because who knows what suggesting that animal tissue not be used, what areas that is getting into that we are not thinking about.

DR. GAMBETTI: How about using this second point to recommend and not to use ruminants in general, whether they are from BSE or non-BSE countries, in other words as a general recommendation?

DR. BOLTON: That was the general recommendation. However, then we end up with the exceptions for hair, hide, gelatin; what did I miss, feathers, fetal calf? Fetal calf is not a source for production of amino acids though.

DR. GAMBETTI: In the case of the ruminants.

PARTICIPANT: I would ask you please, we are not asking for reconsideration of the safety of gelatin which we have considered at length, of gelatin per se which we have considered at length in the past. In 1997, we issued guidance saying that bovine gelatin regardless of whether it is from bones or hides will not be considered acceptable in injectable, implantable or ophthalmic products, and we stand by that position. We are concerned about three things, one the possibility that a hide would be contaminated with high-risk material and two the difficulty in distinguishing after the fact between what is hide gelatin and what is bone gelatin. Of course, our level of responsibility for childhood vaccines is extremely high. I don't anticipate that we will change that policy.

DR. BOLTON: I am confused now. You have left me definitely confused. Is that --

PARTICIPANT: -- hide gelatin versus bone gelatin we are asking you not to consider that question.

DR. BOLTON: But as a source material for amino acid production?

PARTICIPANT: No, for gelatin.

DR. BOLTON: Okay, I think we are here only dealing with what tissues might be used as source material for production of amino acids following acid hydrolysis. So, I don't know that anybody would use gelatin as a source material. I am not sure, but I guess Lisa is nodding her head yes.

DR. FERGUSON: Yes, actually I think one of the manufacturers said that that is -- they are currently using porcine gelatin.

DR. BOLTON: Okay.

DR. ROOS: I think there are two reasons why we suggested validation. One was perhaps as a little bit of a discouragement to manufacturers and second for the potential of increasing the safety here and first really intrinsic in what David Asher said is that gelatin is not exempt and it is actually the source material for these amino acids at times.

We left the issue of validation very vague, intentionally so, and I think I would let the FDA decide what kind of validation might be required. In other words if

it turns out it is gelatin material maybe they want more validation than if it is some other starting material from the cow.

I think, also, validation could be just assuring everyone how amino acids are actually involved in the preparation, how big is it. So, I am comfortable with keeping it as a vague recommendation that some validation be placed if a bovine product from a non-BSE country is source material for amino acids.

DR. BOLTON: I see a non-Committee member that would like to say something.

Bob, briefly?

PARTICIPANT: I would like to revisit my remarks earlier and that is it would be very reassuring I can tell from listening to the Committee to actually have a scientifically approved basis for making this decision. Everyone has some residual discomfort with the idea that maybe these things won't work and there is a good reason for that.

Who would have expected that you could get survival after 138 degrees for 2 hours in some of David Taylor's experiments? Not very much survival but there is some. We do know that 100 degrees by itself is not totally effective. Low pH by itself is not totally effective. It seems to me when you put them together you are likely to get

something that is very effective, but it hasn't actually been done. I haven't done that experiment, and I don't know anyone else who has, and it is a very straightforward experiment. We should at least, it seems to me you do have a right to ask for at least that, that a simple experiment like that be done to reassure everybody that actually the premise that we are all presuming is true is in fact true.

DR. BOLTON: I think what I would like to do now is at least take a vote on that first summary --

DR. WU: Excuse me, could I request a clarification on behalf of CDER? Because of No. 1 asking that bovine-derived, specifically indicating that it is ruminant, so, I would like a clarification that a recommendation based on No. 1 is the ruminant.

DR. BOLTON: We have already voted on Question No. 1 as worded by the FDA and that specifically says, "Bovine derived amino acids from BSE countries." We voted that the manufacturing process does not minimize the risk to allow those to be used. However, we are now considering the question of whether or not the Committee would recommend that the FDA not allow ruminant source tissue from BSE countries in the manufacture of amino acids.

DR. WU: Okay, so, it is for the bovine derived.

DR. BOLTON: Correct, and I think I would like the vote on I guess what would now become the second question

but is part of my four-part summary which we may only get to one part of, and that is as I stated that the Committee recommends to the FDA that ruminant source tissue not be used from BSE countries as a source material for production of amino acids by hydrolytic procedures or something to that effect.

DR. BELAY: Are we putting the exemptions like the milk exemptions for example in that question?

DR. FERGUSON: I understood FDA is saying that that is sort of inherent that the milk exemptions are sort of inherent, correct?

DR. BOLTON: This is ruminant source tissue from BSE countries, not non-BSE countries. Okay, so this would not, I don't know if it would include --

DR. BELAY: What I am asking is currently we are for example, I think importing milk products from BSE countries.

DR. BOLTON: Okay, I see. So, those are inherently excluded already anyway.

DR. FERGUSON: That is what I thought I heard Gerald say is that that is already excluded from their restrictions anyway. So, my point earlier perhaps was unnecessary.

DR. FELDMAN: Just to clarify milk is already excluded and is allowed to be used in the production or used

for drugs in general, is considered a very low risk or non-risk tissue as determined by science and this Committee and should not be a subject of these discussions unless you feel that you want to change your opinion.

DR. BOLTON: And what else falls into that category? Gelatin?

DR. FELDMAN: Tallow derivatives, hides from live animals or not hides but hair from live animals or I believe it is hides from animals where the heads were not -- not for injectables. That is a different issue. So, I guess it is just milk products and hair from live animals.

DR. LURIE: Back to the question from the gentleman from CRH about the ruminant versus cattle. It does actually seem very logical to me No. 1 to say no ruminants from countries that have BSE-infected animals. I mean it is a little bit unfair to French sheep I guess is the way I see it. It is almost as if French sheep are being tarred by the fact that they have got some infected cows. It doesn't seem completely logical to me.

DR. BOLTON: There is some logic in there, Peter, and that is the question of whether or not BSE can be passed on to sheep and be masked as scrapie and yet actually have the infectivity range, the host range of BSE which would then possibly be infectious for humans.

PARTICIPANT: The Committee reviewed that a couple

of years ago.

DR. BOLTON: Okay, can we do this without it becoming extremely complicated? The question is should the Committee recommend to the FDA that no ruminant source tissue with the exceptions noted previously which I hope somebody has written down be used from BSE countries for the production of amino acids.

Can we take a vote?

DR. FREAS: Dr. Roos?

DR. ROOS: I think the answer is yes.

I don't try to sway your vote, but I just want to make sure that I am answering this appropriately.

DR. BOLTON: A yes answer is that we are recommending that ruminant tissues not be used.

DR. FREAS: Dr. Ewenstein?

DR. EWENSTEIN: Yes.

DR. FREAS: Piccardo?

DR. PICCARDO: Yes.

DR. FREAS: Dr. Crawford?

DR. CRAWFORD: Yes.

DR. FREAS: Dr. Belay?

DR. BELAY: Yes.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: Yes.

DR. FREAS: Dr. Nemo?

DR. NEMO: Yes.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Dr.Blackwelder?

MR. BLACKWELDER: Yes.

DR. FREAS: Dr. Stroncek?

DR. STRONCEK: I think this is the question we voted on last time, but yes.

DR. FREAS: Dr. Bolton?

DR. BOLTON: Yes.

DR. FREAS: Dr. Lurie?

DR. LURIE: Yes.

DR. FREAS: Dr. DeArmond?

DR. DE ARMOND: Yes.

DR. FREAS: Ms. Walker?

MS. WALKER: Yes.

DR. FREAS: Dr. Priola?

DR. PRIOLA: Yes.

DR. FREAS: Dr. McCullough?

DR. MC CULLOUGH: Yes.

DR. FREAS: Dr. Leitman?

DR. LEITMAN: Yes.

DR. FREAS: Dr. Cliver?

DR. CLIVER: Yes.

DR. FREAS: Dr.Ferguson?

DR. FERGUSON: Yes.

DR. FREAS: There were 19 voting. All 19 voted yes.

Oh, excuse me. Now, we may go to opinion from the industry.

DR. PETTEWAY: I will give an opinion this time and that is when you are talking bovines it is very simple, I think, and very straightforward but as you expand it to ruminants I am going to agree with Bob Roher(?) and there is a couple of things. One is understanding exactly what the process is and the validation of the process and the other is generating relevant data to make the decision on and we don't have relevant data for either one of those. So, I think that you just need to keep that in mind when you are making these sorts of decisions that there is a way to generate relevant data that can be useful in making these kinds of decisions.

DR. BOLTON: Very good. I see that it is after three. So, we should adjourn now.

We do have, I guess, the consideration now as to whether we want to deal with this question of encouraging non-ruminant source material. Perhaps that is a moot point. It may not be worth all the hassle and back and forth that we would have to do to come to some conclusion and with respect to the recalling of products perhaps we could defer

to the FDA's question No. 2 as Bruce has suggested earlier and that question is if not Question 1 which we voted no on does the Committee feel that there are circumstances where the risk/benefit ratio would still be in favor of a subject receiving the product where suspect amino acids had been used in its manufacturing process. As I think we discussed there will be circumstances, probably most circumstances where the risk/benefit ratio would still be in favor of the subject receiving the product. So, perhaps we can take a vote on that in lieu of going through specific recall recommendations and I think at that point the FDA will clearly have a sense of what the Committee thinks.

So, Bill, let us take a vote on Question No. 2 as posed by the FDA.

DR. FREAS: Dr. Roos?

DR. ROOS: Yes.

DR. FREAS: Dr. Ewenstein?

DR. EWENSTEIN: Yes.

DR. FREAS: Dr.Piccardo?

DR. PICCARDO: Yes.

DR. FREAS: Dr. Crawford?

DR. CRAWFORD: Yes.

DR. FREAS: Dr. Belay?

DR. BELAY: Yes.

DR. FREAS: Dr. Williams?

DR. WILLIAMS: Yes.

DR. FREAS: Dr.Nemo?

DR. NEMO: Yes.

DR. FREAS: Dr. Gambetti?

DR. GAMBETTI: Yes.

DR. FREAS: Dr. Blackwelder?

MR. BLACKWELDER: Yes.

DR. FREAS: Dr. Stroncek?

DR. STRONCEK: Yes.

DR. FREAS: Dr. Bolton?

DR. BOLTON: Yes.

DR. FREAS: Dr. Lurie?

DR. LURIE: Yes.

DR. FREAS: Dr. DeArmond?

DR. DE ARMOND: Yes.

DR. FREAS: Ms.Walker?

MS. WALKER: Yes.

DR. FREAS: Dr. Priola?

DR. PRIOLA: Yes.

DR. FREAS: Dr. McCullough?

DR. MC CULLOUGH: Yes.

DR. FREAS: Dr. Leitman?

DR. LEITMAN: I just want to clarify it is not any circumstances. The Committee discussed all circumstances. We feel this is not an issue. So, my vote is yes but just to

clarify it for the FDA we don't have any difficulty with that. So, it is all circumstances.

DR. FREAS: Cliver?

DR. CLIVER: Yes.

DR. FREAS: Dr. Ferguson?

DR. FERGUSON: Yes.

DR. FREAS: And the industry opinion?

DR. PETTEWAY: Yes.

DR. FREAS: Okay, there were 19 yes votes on that question.

DR. BOLTON: Does anybody want to change their vote if we change the wording from any to all?

DR. FREAS: I think everybody is satisfied with that.

DR. BOLTON: I believe we have come to the end of our day's work.

Question 3 then becomes moot and the FDA did not ask us to deal with Question 4.

So, we will reconvene tomorrow morning at 8 a.m., to deal with topic 3 and it is a much better job of keeping on time today than our last meeting.

I thank you all.

MR. BLACKWELDER: Could I change my vote on one of those?

DR. BOLTON: As long as the meeting is in session.

What would you like to change your vote on?

MR. BLACKWELDER: The ruminants from BSE countries. If I am correct it seems like the science is that we don't have evidence for saying that. At least that is what a couple of people have suggested. If that is correct I would like to change my vote to no.

DR. BOLTON: We could debate that ad nauseam, but if you would like to change your vote I think that is fine. So, that would be from a yes to a no.

This meeting stands adjourned until tomorrow morning at 8 a.m.

I thank the Committee members and the members of the public for attending.

(Thereupon, 3:13 p.m., a recess was taken until 8 a.m., the following day, October 26, 2001.)