consequence of having perhaps been present in the calf serum that went into the medium.

If there aren't prions there that can be converted to the Rez configuration, they are not going to propagate. There's not propagation as such in the introduced prions in those cell cultures.

DR. BOLTON: There's somewhat of maybe a dichotomy here. If you look in the normal animal, PrPC is made in many, many different tissues, including heart and skeletal muscle and lymphocytes and a lot of different tissues besides the brain. But it's a curious fact that when you try to propagate prions in these other tissues, it doesn't seem to work.

It seems to work really well in central nervous system tissue and not very well in anywhere else. So right now in the absence of actual data, my guess would be that propagating prions accidentally in cell cultures would not be a problem, but there is a clear path to obtaining that real information, although it would be time consuming and somewhat expensive, but that information could be had.

DR. CLIVER: But you can't propagate polio virus in a monkey's kidney either. Yet we're doing a very good job of propagating polio virus in cells

derived long ago from monkey kidneys.

So I think appeal to the original monkey is probably not very useful in this case. We don't know how the cells that we now call the vero line were selected from one fortunate or unfortunate but not immortal African green monkey.

So I think it's better to focus on the line as we now use it and not think so much about whatever was swinging from a tree 25 years ago.

CO-CHAIRMAN GREENBERG: I'm going to switch away from the topic that I don't know anything about, propagating prions, except my own, and try to get back to the question.

It seems to me, Paul said it very clearly. The risk in fetal calf serum -- I think I'm just going to assume that all of you around the table heard exactly what I heard, that the risk is going to be very low, but potential -- there is potentially some risk.

The question that I come up with is it sounds like, if you use fetal calf serum from a country or geography where there is no disease, you've lowered that risk, that potential risk, a fair amount more than if you used it from a place like the U.K.

I don't see a convincing reason, given the

world surplus of cattle, that we need to say we need to maintain our ability to use -- I don't have a good rationale for saying why I want to use fetal bovine serum from the U.K. or from France or reserve the right to do that, when I have this universe of cattle out there that would lower the risk.

So now I haven't addressed things that are already in the freezer that were made in the past, but to start things I would say I can see no reason in a go-forward way that one would ever use serum from those countries. But I could be convinced otherwise.

DR. SNIDER: I would agree with that, Harry, and I think that I would go further in terms of thinking then about the stuff that is in the freezer and say let's get rid of that, too, but not at the expense of having -- in a radical manner that would expose kids to the risk of vaccine-preventable diseases. But then the questions I was posing earlier were because I was trying to think more broadly and strategically about this issue for the future, because I don't know what's going to happen.

I don't understand these set of infectious diseases very well, and I don't know what's going to happen in Australia or New Zealand or the United States with regard to TSEs. I hope that what's been

put in place will prevent those from occurring, but in case we're wrong about that, one of the things I was trying to get at is, is there a way to develop a process that would remove prions and then the folks also getting into a discussion, is there a way to sensitively determine that you have removed them or that they are not there, and shouldn't we be moving in the direction of trying to find those methods for manufacture and for analyzing materials?

CO-CHAIRMAN GREENBERG: I'm in agreement, Dixie. Now I'm going to stop right now. But given that, I guess it's Dr. Trouvin who spoke for the EU. So I must be missing something, because one of the things that he says, materials may also be sourced from countries where low numbers of indigenous cases have occurred.

So that's an EU point of view, and I don't understand the rationale for that point of view. Why give yourself that out? Is he here?

CHAIRMAN BROWN: Dr. Trouvin? Is he still in the audience? Yes.

CO-CHAIRMAN GREENBERG: So did you understand my question?

DR. TROUVIN: Yes. The rationale: It's clear that, first of all, we have to consider whether

there is even the risk in using such tissue or such fluid. If there is a -- that there is no risk that the level of risk is theoretical, then why to add an additional criteria such as the geographical region for which, even for this criterion, you cannot have an absolute assurance even of the origin for a country.

CO-CHAIRMAN GREENBERG: Okay. So that's what I thought you were thinking, actually. So I disagree with that rationale. Unless you could tell me compelling reasons that fetal calf serum in Austria was 100th the cost of getting it from New Zealand, I don't see a reason to support the Austrian fetal calf serum industry, you know, saying that, well, I don't think there's any risk at this point of serum being contaminated or you show your 10^{-20} slide.

From my standpoint -- and this is the last I'll say -- listening to all this, it looked to me like we're never going to get past it until we have better assays the feeling that there's some incredibly small risk of transmission from fetal calf serum where there is this disease in the cattle in that country.

Since we have a way of avoiding that risk, why not do it? I'm done.

CHAIRMAN BROWN: Yes. I think I'll have just a second. We are really always talking about the

same question in different dress. That is, even if I know that, let's say, a chicken had the flu and I know that chicken flu is absolutely not a human pathogen, given the choice between that chicken --

DR. FERRIERI: Be careful.

CHAIRMAN BROWN: -- and a chicken without--

DR. FERRIERI: You're in very dangerous grounds, really. Don't talk chicken flu with our group.

CHAIRMAN BROWN: -- I would still prefer a healthy chicken. I'm not trying to get into questions about whether chicken flu is a pathogen for humans or not. It just came to the top of my head, but the principle is there. If I have something which has a disease for which there is absolutely not a shred of evidence that it's a human pathogen, and I still know it has the disease, and there's a choice between that and something that doesn't have the disease or something, it's just human nature to want the one that's healthy. That's a fact. go ahead.

DR. KOHL: It's sometimes nice not to know too much about some things. So as you said earlier in a different way, the science doesn't become a barrier.

We're balancing two major problems. One

is an incredibly small risk of a terrible disease, and we've heard different analyses today going from 10^{18} or 10^{10}. They are really teeny, but one is much, much higher than the other, and next week it may be 10^{5}. I don't know, but there is a risk.

Obviously, as Harry has said, as Dr. Brown said, if we can move to a less risky system, we ought to do it, and I don't see why we are not doing it. Now we are not doing it, because the other component is something we haven't heard much about or something that is not forthcoming at this meeting, unfortunately. What is the risk right now of moving to a safer situation where we don't use any material that was sourced from BSE countries?

That's where we need to know how quickly the manufacturers can shift over, and whether there is any kind of a production lag, and whether there will be uncovered children, because that's a real risk. I don't want to see measles or polio in this country, or more pertussis.

So that piece of the equation we desperately need, either from the CDC or from the manufacturers, and several of us have asked that question and it's not been forthcoming.

CHAIRMAN BROWN: I have something to say,

but I'll hold off, because we have two other comments, at least. Yes, please?

DR. DAUM: I would actually like to hear responses to Kohl's comment. He mentioned that he's sure that there is a risk. I'm not convinced after what I've heard today that there is a risk that we can actually measure, but I am concerned about the safety of the vaccine supply that we put into children.

So if there might be a risk, I'm almost willing to stipulate that there is for the sake of this discussion. But I would like to temper that with Dr. Orenstein's presentation this morning and a piece of information that I've calculated while we've been talking.

It seems to me that the highest risk that's been presented today is about one child or one dose in 40 billion being infectious. If that's true, and the U.S. birth cohort is about 4 million, and each child gets ten injections of this stuff, it would take about 1,000 years at that point to have one child get an infected dose.

So that I want risks to be zero, but I do want to call attention to the fact that we're dealing with exponential numbers here, 10^{-10}, 10^{-18}. These are incredibly low numbers, and I think this calculation

gives some sense of where the actual risk to an individual child is. However, I, like everybody else here, want it to be zero.

I think that Dr. Greenberg's comments would go a long way, if it's feasible from a manufacturing perspective and FDA perspective, would go along way toward acknowledging this committee discussed this; this committee had appropriate concern about it; and took a reasonable step without all the information that we need to define things to drop that risk a whole lot further.

So I would like to hear whether out-sourcing the serum to -- the serum source to a country where there is no disease at the present time, while a lot of the missing science gets filled in, can be accomplished.

CHAIRMAN BROWN: I think probably no one -- go ahead.

DR. EGAN: Could I just address a couple of the issues that have come up. With regard to the manufacturing, the actual production of the vaccine, fetal calf sera is sourced from countries such as the U.S., Australia and New Zealand. No materials from Europe are used in the actual -- you know, the production.

What we are referring to here are the master seeds and the working seeds. Those can't be changed. What we're talking about is, first of all, whether or not we need to change the master seed, which will take some time -- it's doable -- with regard to the fermentation and the use of bovine broths.

All of those sources, you know, are being -- have been changed and are being changed, and the issue is what to do in this interim, this period of about a year, while new lots of vaccines would be produced, formulated and tested and released.

So there is not a continued use of fetal calf serum from U.K. and Europe in the production. The fetal calf serum refers back to these master and working cell banks.

CHAIRMAN BROWN: I may not understand. What I interpret you to say -- to mean is that, say a year from now, all of these things that are being addressed in the questions will have been taken care of. That is to say, working seeds and master seeds will be changed. Fetal calf serum will be resourced, ta-da-da-da. What do we do in the year -- in this coming year? I mean, what are the options? Are we going to --

DR. EGAN: Yes. I meant not necessarily certain for the fermentation and the use of the beef broths that we've heard discussed by Dr. Vann and by others. Those will be changed, and it will probably be on the order of a year to have new vaccines from them on the market.

If manufacturers have to change the master seeds, I think that will take longer to re-derive those.

CHAIRMAN BROWN: Well, let me ask you and the committee a question then. Let's suppose that one of the seeds, whether it be a working seed or a master seed, was prepared, let's just for fun say, in 1985, and amongst the materials to which it was exposed in the course of its being produced was a meat broth sourced from the U.K. which, I think, we've heard today, if I'm not mistaken, might have been the squish from mechanically recovered meat which would include spinal ganglia and spinal cord.

What you're asking is what do we do with that master seed now, or what do we do -- You're saying it's going to be replaced but in a year, and so I guess what you're asking is what do we do with the vaccines that have been produced from this master seed, that are still in circulation? I mean, is that

the question?

DR. EGAN: Yes, as well as whether the committee feels there's a significant risk from the master seeds to warrant replacing them. I think some of the estimates that you heard from us on, you know, the risk assessments that we did for the master seeds were on the order of 10^{-18}.

CHAIRMAN BROWN: So you're not saying that all of the manufacturers are going to replace their master seeds. You're asking us to recommend or talk about whether or not we think it should be done.

DR. EGAN: Yes. The fermentation process, use of bovine derived material -- that is being done now. That is taken care of.

CHAIRMAN BROWN: All right. The fermentation process and bovine derived media -- that's being done. The master and working seeds is still at issue. Is that right?

DR. EGAN: Yes.

CHAIRMAN BROWN: And the formulation of the final product.

DR. EGAN: And the issue there was the use of fetal calf serum.

CHAIRMAN BROWN: Right. Comments? Discussion? Yes?

DR. BURKE: I have a question that would be a generic question for the manufacturers. It seems almost an oxymoron to say that you can replace a master seed and still have the same vaccine. Most of the time when you change a master seed, you're changing a fundamental property of a vaccine.

To say that that could then continue to be licensed under the previous Phase I, II, III and efficacy seems almost incompatible, to me. I would ask my colleagues at both the FDA and the manufacturers, do I understand this correctly, that a change in a master seed would almost by definition mean a need to relicense, in which case it would be impossible.

CHAIRMAN BROWN: Yes, Catch-22.

DR. BURKE: This is a question. I'm asking both the FDA and the manufacturers.

CHAIRMAN BROWN: Okay. Do you have a choice of first response?

DR. BURKE: I'd like to hear from both.

CHAIRMAN BROWN: FDA first or it doesn't matter?

DR. BURKE: I defer to the Chair.

CHAIRMAN BROWN: FDA, as long as you're standing up.

DR. EGAN: Yeah. I mean, the change in the master seed is extraordinarily difficult, and I guess we're talking about, in the case of viral vaccines, re-deriving the seed from clones, if they exist, or plaque purifications. Again for bacterial vaccines, again trying to do purifications through growing up, dilution, pulling out single colonies, you know, isolating it, regrowing it again and again.

CHAIRMAN BROWN: And the same thing doesn't apply to working seeds. Working seeds are not a problem.

DR. EGAN: The working seeds are not a problem, because you just re-derive a whole bunch of those with the masters, and that can be done.

DR. FERRIERI: But what would you be requiring to do? Would you be requiring the manufacturers to submit for all the new trials? I don't think that's what you would be requiring them to do, is it?

DR. EGAN: Submit for -- You mean new clinical trials? Would it require a new IND?

DR. FERRIERI: Are you going to need to go through all the Phase I, II and III?

DR. EGAN: No, I don't think so.

CHAIRMAN BROWN: So what you're saying is

that, supposing -- just supposing the committee felt very strongly that all of the master seeds ought to be replaced. You are saying that the FDA approval of such master seeds would not be a standard approval process?

DR. EGAN: Well, it would have to be a supplement that would be submitted to the license. It would have to be dated to show the identity to the original material.

DR. BURKE: How would you guaranty identity?

DR. EGAN: Well, I think this is a bridge that we're going to have to cross. I'm not -- You know, in some case it could be through sequencing.

CHAIRMAN BROWN: Dr. Ewenstein?

DR. EWENSTEIN: Well, I wanted to contrast what we are trying to do today to --

CHAIRMAN BROWN: Yes, any of the manufacturers, please.

MR. STEPHENNE: Yes. Jean Stephenne, SmithKline Beecham. I would like to make a few clarifications.

The first one, I don't think that any manufacturer is using any serum coming from BSE country. So that's the first point, and I think there

has been confusion during the discussion about that.

So as you know, when we manufacture vaccine, we start from the working seed. We grow the cells, and we use bovine serum. This bovine serum since 1990 has been changed to the source which are non-BSE countries. So I want to avoid the confusion there.

Secondly, when you manufacture vaccine, you need master seed and you need working cell bank. Then if you look back to the history, what has happened in the Seventies or Eighties when these vaccine were developed, that's really the fruit of research. Right? So it has been years of research to develop these vaccine.

So if today you take, for example, MRC5 cell line, which I use for production of hepatitis A vaccine, this cell line were discovered in the U.K. and developed in the U.K., and they have a certain history, and you cannot change that history, which means you have to go back to the master cell line. That's the only thing you can do, but you cannot terminate all the history.

Two, when you look to history, let's say ten years ago the way we were controlling productible bioengineering is totally different than what we are

doing today, which means that the manufacturer of amino acid has changed the process also during the last 20 years and the last ten years.

Why? Because attention has been given to BSE, which means when you speak about fetal calf serum, you need also to speak about other ingredients, for example, gelatin-derived product, whether gelatin produced 20 years ago is safe as bovine serum?

So it means we need to address working cell bank and working seed virus. Can you change it? Yes, we can do it, and the process is ongoing and in discussion with health authorities.

Then can you change your master seed? For us, it's a new development. It is the development of a new vaccine, because I don't think that someone can guaranty that we'll do all the in vitro tests to prove that the vaccine you have done and the new strain you have done is similar to what you have used in the past. So you have to re-do everything.

So I think we need to in the discussion phrase, what do we use in routine production? Can we change a working cell bank? Then what do we do for the master cell virus or cell bank? And when addressing that, I think that's a question which must be addressed for all manufacturers, not the European

manufacturer.

Why? Because who can guaranty that 20 years ago a U.S. manufacturer who was buying U.S. serum or was buying U.S. amino acid was -- there was no certificate of origin. There was, I would say, less control of manufacture of these products than today. So I think we have to address it globally as the whole industry. Thank you.

CHAIRMAN BROWN: Thank you very much. Dr. Ferrieri?

DR. FERRIERI: I think nothing stirs our blood more than the possibility of adventitious agents in our vaccines and the enormous problems that this imposes on manufacturers as well as the potential for undermining our vaccination effort and the confidence of parents and consumers on behalf of recipients of vaccines.

I feel a bit compromised today, as Dr. Lurie had mentioned earlier, in not being able to ask certain very specific questions. So I think that I'll try to stay away from anything controversial.

From a theoretical standpoint, I don't understand why we can't test these master seeds and at least have some confidence that using the best assays that might be available, that we might feel secure

that they do not display any infectivity potential.

I applaud the manufacturers who have presented their plans to replace all bovine sources, but realistically, we know that there may be some aspects of the whole process that will not be able to be replaced.

So based on everything I've heard today, I do not see -- and I'm fairly conservative and very interested in the safety of all that we do here, but I don't see that there is anything we've heard that impugns the integrity of vaccines that are on the shelf to any significant extent at all, and that we need to solve the problem and move forward.

We have solved other problems of a tougher nature within the past five years at the VRBP Advisory Committee, and this one will be solved as well. I guess I'm an optimist and know that CBER and all of you will be able to meet the kinds of requirements that we need. But I don't think we should be overhysterical about the current problem and that the current master seeds are likely to be pretty intact.

CHAIRMAN BROWN: You raise an interesting issue. The next one is Dr. Ewenstein, but the issue is today, is there anything that the FDA might do, from the committee's perspective, about risk on the

shelf, so to speak, versus the future, and what might be done in terms of a word that we haven't heard so far today but this committee is very familiar with, validation tests. For example, taking a master seed, spiking it with a bovine strain, processing it, and then inoculating the final product into the most susceptible host, which would be a cow or a bovinized transgenic mouse.

That's a kind of two-year experiment, but two years or three years from now, as is usual in these discussions, we may have the information that we need now, but at least it would be something.

Other comments and questions? Dr. Ewenstein?

DR. EWENSTEIN: Well, I was beginning to say I wanted to contrast what we were trying to do today to what we did in the donor deferral question. I think there at least we had the ability to look at the risks and the benefits, and we tried to find a point at which we would not seriously interrupt the blood supply while trying to reduce a theoretical risk.

I think we're accepting the fact now that we don't have that other side of the equation today, and we can only suspect that the impact of losing

these vaccines for one or more years would be large, but we have no specific number on that.

I don't think we've heard anything today that would justify a large risk on the loss of the vaccines. I think it should also be put into context that you have to compare the risk of catching TSE through a vaccine, if you will, to the real risks that we already know exist that we're willing to balance, and that includes idiosyncratic reactions and allergic reactions and -- well, we heard about shingles and the like.

So these vaccines are never going to be risk-free, as is true of anything in medicine, and I don't think we heard anything today that would raise what we're talking about here with TSE above the risks that we know we are already taking.

All of that said, I think that, if there are things that can be done in the interim -- the manufacturers have talked about some of the things that they've been done -- that they are doing, rather, that have been done. I would encourage that, and I would hope that the FDA would enforce the guidance to that degree.

I suspect that the sensitive test that we're looking for for TSE is going to come around

before we could perhaps develop the new vaccines that have been at least theoretically discussed, and that we are likely to get to the answer more quickly that way than we are to start from scratch in developing all new vaccines.

DR. MODLIN: I'd like to agree with the last two comments almost completely. I think there's a fair amount of room here. I was going through the same calculations that Dr. Daum was with respect to the likelihood of observing a case anytime in the near future, and it appears to be so remote that I think that there's a considerable amount of room and confidence that there is -- we can take, I wouldn't say a casual approach to it. That's the wrong word to use, but can have some confidence that considering the alternatives, considering the alternative of seeing the return of vaccine-preventable diseases even in a small number of children, which would be likely or certainly be a much higher probability event than, I think -- I would take a measured, thoughtful but direct approach that Dr. Ferrieri suggested.

That is to test what we can test and derive what information we can from that, and then to proceed further. I would just point out that one of the vaccines that was under discussion today is IPV.

If the WHO eradication effort continues to go as successfully as it has in the past, there's a likelihood that -- or use of IPV that we'll be using in the future will be finite and that we, you know, hopefully, will never have an opportunity to see whether IPV, no matter how it's manufactured, is associated with an adverse event from adventitial reagent.

So I think a measured approach to assessing what risk we can and taking the steps to remove what we can to reduce the risk makes a lot of sense. But I certainly would not encourage anything else.

DR. ROOS: I think we have safe vaccines now with respect to perceived dangers of spongiform encephalopathies, and what we really have is perhaps a perceived risk. It would be great to get rid of that perceived risk, but the question is what's the downside of making new master lots of cells and virus seed.

It sounds to me, first, as if there are going to be regulatory issues that are going to be rather onerous, that there will be difficulties establishing secure, safe cells. That is, the histories of these cells may be controversial, the

fact that there is perhaps mysterious histories about some of the lots that were used in any of these cells sometime in the past.

I think the third issue, which is an important one, is that these new cells and virus seeds won't really have the history of safety with respect to many other viruses and adventitial agents that we presently know with vaccines today.

So there's a tradeoff here in potentially getting virus that has no -- that is less likely to have fetal bovine serum from a U.K. source, but the tradeoff is that we really don't have the safety record for these new established vaccines. So I think that, in order to decrease perceived risk here, we may be taking new risks that are unknown.

CHAIRMAN BROWN: Just a second. Ms. Fisher, did you have a question that I haven't been paying attention to?

MS. FISHER: I do have a comment. I think that Dr. Berkower summed it up best, at least for me as a consumer rep, when he said there are many factors we would like to know but don't know at this time. What I've learned here today is that when bovine derived materials are used in vaccine production, especially materials from countries where BSE is known

to exist, there is at least a theoretical risk of TSE transmission and that this risk is made more possible by the technology limitations to detect adventitious agents.

I think that, if there is a risk, even a theoretical risk, from a consumer's standpoint that you have to tell the people who are using the product. There has to be full public disclosure, and I would encourage the FDA to look at requiring the manufacturers to have something in the product manufacturer insert to reflect this theoretical risk.

CHAIRMAN BROWN: Thank you. That is an interesting issue. Of course, it's one of the FDA options to be able to do it, and I'm sure as a consumer rep you recognize that the likely reaction -- and I'm all for public disclosure -- of a letter which says "Dear Doctor, it has come to our attention recently that this vaccine contains fetal bovine serum that was processed from Great Britain which has, as you know, killed a number of people from mad cow disease. We thought you ought to know -- You know, you wonder whether or not the risk is sufficient even to cause this much anxiety, because it does.

MS. FISHER: It may be a difficult thing to address, but I don't think that -- I think the

public trust is important and, if you're truthful with the public and forthcoming with the public all along the way, then there are no surprises for anybody in the future.

I think that people cannot be elitist and decide what is best for other people. You have to have full public disclosure about even a theoretical risk, and I think in the long run it's going to serve the vaccine program better than to basically have people be finding out that we knew but didn't tell.

CHAIRMAN BROWN: Yes. I, a hundred percent, absolutely agree with that, and it's a long process of education and people have to -- You have to take the flak for a while until people understand that when you're telling them that there is a theoretical risk, that that's exactly what you mean, there's a theoretical risk. And they gradually begin to appreciate the remoteness of that risk and, therefore, accept it. But I agree that it's entirely better to do it that way, accept the reaction you're going to get from that subset of the population that always at zero risk as the only alternative, and gradually they will come to understand that there really wasn't any risk, but still --

MS. FISHER: At least you were honest. At

least you were above-board.

CHAIRMAN BROWN: Yes, right, exactly. At least you were above-board. Go ahead, please.

DR. LURIE: I think those are very important points. Let me just make one sort of introductory point and then follow up on Ms. Fisher's point.

As I see the very worst case scenario here, which is not, of course, the only one, and Dr. Vann's presentation, the fermenter under the worst scenario -- and again, it is the worst scenario -- is a five times 10^{-8} probability of a single dose being infected. That's one in 20 million. It's not one in 40 billion, and one in 20 million -- Again, we don't know how many vaccine doses, because we don't know which vaccines, etcetera, etcetera -- points I've made before.

Certainly, that doesn't take very long for 20 million shots to be administered in this country. But having said that, I think that Ms. Fisher's point is absolutely right on. I think that the fact of -- There are two reasons to disclose. One is a moral one, that the patient would like to know and, I believe, has the right to know about a risk like this.

Certainly, I would like to know if I had

been exposed to a minimal risk or not. So I think that's a moral issue, and I do think we should steer away from paternalistic ideas about what is best for patients. I think that's the sort of thing this country has been leading the world in moving away from.

The second point is, frankly, a political one. The fact of the matter is that in this room today there are a number of members of the press, and they are going to write stories about this, and those stories are going to be on the Internet by tomorrow, and they are going to be out there for people to talk about.

It is going to do no good for this committee or the public health or for public confidence in vaccines for that kind of stuff to be out there and we taking a position that somehow patients should not be adequately informed in some fashion.

So I think that, for political reasons as well as moral reasons, we do inform. The question to me is not so much whether to inform, because it's informing via Reuters and the AMA News versus informing by the FDA, the manufacturers or the doctor. That's really the question.

So I think the question we should be asking is how to inform, and my own feeling is that a letter to doctors explaining this can be written. It would be difficult to do, but I'm sure the FDA can write a letter that will explain how small the risk is, but still provide the information to doctors who will need to be answering the questions posed by the patients who read about this on the Internet tomorrow.

CHAIRMAN BROWN: Well, as this is one of the options that the FDA has and the question has come up, I think we should clear the decks and ask for any other comments about this particular issue. That is to say, shall we say, quote/unquote, "informed consent." Dr. Ewenstein?

DR. EWENSTEIN: Well, I agree that the facts are already out there essentially, as you are saying, and I think that adding it to the package insert, as long as it's put in the right context, makes a lot of sense.

I'm wondering really whether a "Dear Doctor" letter which has a certain amount of urgency attached to it isn't overkill, and I think it's also important that we not just be a neutral filter. At the risk of sounding somewhat elitist, it is our job to make recommendations and to put things in context,

and to put information out there without a recommendation is really betraying the trust that, I think, we have here to make a recommendation.

I think that it should be stated that, although there is this theoretical risk, that the best calculations that we can put forth -- and I am somewhat encouraged that, although there is a wide range, that none of the calculations, whether they be from industry or from various government or impartial sources, one might say, exceed, I think, by any of our calculations the benefits, and by a very wide margin.

I think it's important that it be stated that way, just as when giving a vaccine it wouldn't be fair -- forget the TSE risk -- to say this is a risk-free thing. Okay? If somebody asks you, you would have to be honest and say that rarely people have severe reactions, but extremely rarely, and not to the point where we stop giving vaccinations.

I just think it needs to be put alongside a recommendation that no change in practice is indicated.

CHAIRMAN BROWN: I have a sense that the entire committee feels essentially as Dr. Ewenstein just expressed. Is there any dissenting view? If there's not, I think the FDA has one answer from

today's discussion, and now we will have another comment. Yes?

DR. HUANG: No, I completely agree with the last speaker, but I think this is the right time to say that it's terribly important as we look at the data that's been presented today that we recognize that there is still a lot to be found out, and although some of the experiments that have been suggested, I would say, are really trying to prove the negative and that we go out and ask people to spend their whole careers trying to prove the negative, that's not going to work very well.

However, there are a few areas that have come out today which, I think, it's important to stress, and some of it has been discussed at great length and others have not.

There are three areas which I think are extremely important. That is: Understanding inactivation of the prion material; providing -- continuing the surveillance that we have had in the animal population; and improving the diagnosis.

I think that there are areas which we can pursue very effectively that will help in surveillance, help in inactivation, and improved diagnosis.

CHAIRMAN BROWN: Inactivation may be a dead issue, in a sense. I mean, there's been a tremendous amount of work over the past 30 years on inactivation, and the bottom line is that virtually anything that inactivates this agent will inactivate the biological activity of anything that it's in.

So that's probably not the most fruitful line of future research to follow. Surveillance, certainly, will be continued, and as you've heard, some of the European countries are now doing pilot studies or beyond pilot studies of fairly sensitive tests for the detection of infectivity in cattle.

I guess that's what you're really talking about, diagnosis. Right? The diagnosis of BSE?

DR. HUANG: Well, Mr. Chairman, I might suggest that, for instance, in terms of inactivation that now that we know the sequence, we might have specific proteases or specific sequence binding small molecules. There are ways of looking at that.

I think also, in terms of diagnosis, the whole area of chaperon and interaction of floating proteins with chaperons is worth pursuing. There are areas now in molecular biology that offer whole new avenues, and even quite specifically, when we think about the genetic restriction that we know about now

with PrP gene, that that area can be pursued in detail as well.

So these are just a few that come to mind. I'm sure there will be others that I haven't thought about.

CHAIRMAN BROWN: I really think the diagnosis of BSE is up to speed. I mean, cattle that die and are examined histopathologically and who die or that die from the disease test positive by current tests.

DR. HUANG: Well, yes, I think that that is a good test, but it takes, what, 36 months?

CHAIRMAN BROWN: No. That takes -- That's a PrP detection test. It takes 36 hours. It's a good test.

DR. HUANG: You mean cattle die in 36 hours?

CHAIRMAN BROWN: I'm sorry?

DR. GRIFFIN: You're talking about cattle that are ill.

CHAIRMAN BROWN: Not necessarily, not necessarily.

DR. FERRIERI; In surveillance of herds, you would be doing that.

CHAIRMAN BROWN: That's right. That's

what they are doing.

DR. FERRIERI: And so this is early. I mean, this is how they are monitored, and I want to add that we not be complacent about the purity of what may come out of Australia and New Zealand, etcetera, and that we continue to have molecular monitoring so that we do not make any false assumptions, if products are used from non-European countries.

DR. PICCARDO: I agree with that. I think it's --

CHAIRMAN BROWN: That's Dr. Piccardo.

DR. PICCARDO: Sorry. I agree with that, because as the discussion moves, we have to rely more and more on countries that we suppose are BSE-free. I mean, if they say they are BSE-free, okay, we'll believe them, but there should be somehow a monitor system that keeps the standard very high, because we rely more and more on those. So yes, I agree with that.

CHAIRMAN BROWN: We should remind the committee that Dr. Piccardo's home of record is Argentina. Another question?

DR. PICCARDO: Actually, that has nothing to do with what I just said. Actually, if the people from my country hear what I just said, probably they

will kill me.

CHAIRMAN BROWN: Hold on just a second. Yes, Dr. Almond?

DR. ALMOND: I would just like to echo what Alice Huang said concerning inactivation. One area that I think is very poorly investigated is the effect of acid hydrolysis on prions. I know that -- I spoke to David Taylor recently who, of course, has done a lot of the inactivation studies, and the effect of acid hydrolysis is very poorly studied on prions.

Now that -- We know it's a protein molecule. We know the peptide bond is susceptible to acid hydrolysis. We know that acid hydrolysis is actually used in the preparation of a lot of bacteriological growth media, including, for example, casein hydrolysate, but also things like thioglycollate, hemin and so on involve acid hydrolysis steps.

There is one poster which describes this, and it looks like hot acid really knocks the hell out of prions, actually. Ray may know something about that poster, but I think more studies along those lines would be interesting and might serve a great reassurance, at least on the bacteriological growth media side, that are those media so treated, the risk

from prions goes away.

CHAIRMAN BROWN: We do have information about one strain, which is a relatively resistant strain, which is the hamster strain, an that's unaffected by pH-1. I don't know if --

DR. ALMOND: I think the observations are that cold acid does nothing, but hot acid certainly seems to. And it's hot acid -- The heat -- When you do an amino acid analysis of a protein typically, of course, is by a chemist with heat with acid overnight, and you smash the protein down to amino acids and do your amino acid hydrolysis.

CHAIRMAN BROWN: Is boiling acid compatible with vaccine biological activity?

DR. ALMOND: I just remind you that casein hydrolysis --

CHAIRMAN BROWN: I know. I'm not being smart. I'm asking a question. Is a vaccine --

DR. ALMOND: Well, what you are providing in a bacteriological growth media is a source of amino acid is a source of peptide is a source of protein. It doesn't need to be intact, and certainly the acid hydrolyses that you do use on that just smash the proteins, and that's quite clear in things like casein hydrolysis being a case in point, and

thioglycollate broth as well.

So if you are providing nutrient to a bacterium, then that's fine. Of course, you couldn't do it on calf serum.

CHAIRMAN BROWN: That's what I say. This has to do with the nutrient media, not the bacteria.

DR. ALMOND: Absolutely, on the nutrient media that you feed them with, where it enters into the process. You, obviously, couldn't do it on the calf sera. Wouldn't expect it to survive, but certainly on the nutrient source for the bacteria, that would be a good place to start looking.

CHAIRMAN BROWN: Right. This is a subset of what you were asking, Dr. Huang. Instead of trying to knock out the agent, we knock out the possibility that the agent might exist in media to which it's been exposed. In other words, that you know that the media at least that contacts whatever it is you're making a vaccine from cannot be infectious.

DR. HUANG: Right. In that case, you are knocking out the agent from a nutrient source. I think that there are other methods that one can approach of knocking out the agent from the final product.

CHAIRMAN BROWN: Yes. Two of the most

important things or useful things in general are one normal sodium hydroxide -- pretty tough -- and 6 to 8 moler urea, which oddly enough, does not destroy the biological activity of human growth hormone.

So there are surprises. Yes, in the back? I think your compatriot there had priority.

DR. SLAOUI: I just want to share with the experts around the table --

CHAIRMAN BROWN: Could you identify yourself, please, again?

DR. SLAOUI: Sorry. Moncef Slaoui from SmithKline Beecham.

I'd like to share with the committee again a real life experiment, because rightly so, many experts have stressed how fully sensitive or eventually fully sensitive the detection methods that are available today out there to assess the infectivity of the components involved in vaccine manufacturing.

Well, if we consider fetal calf serum, I'd like to share with you a real life experiment in which 29 million doses of bovine vaccine have been manufactured using amounts of fetal calf serum sourced from the U.K. between 1985 and 1988, i.e., at the time where the epidemic was growing, and it had been

inoculated in -- actually 26.5 million doses inoculated outside of the U.K. in bovine. There has not been a single case reported of vaccine-associated BSE.

I can't think of a larger real life experiment assessing whether fetal calf serum or actually cow serum or adult bovine serum involved in vaccine manufacturing in amounts that are orders of magnitude higher than what we are discussing here can be reinoculated in cattle. So I think that's probably very relevant to the discussion.

CHAIRMAN BROWN: That's very interesting. It ought to go into a letter to Lancet.

DR. SNIDER: How good is the vaccine adverse effects reporting system in cattle? I hope it's better than it is in people.

CHAIRMAN BROWN: Can you identify yourself, and repeat the question, please?

DR. SNIDER: This is Dixie Snider of CDC. The question is how good is the vaccine adverse effects reporting system in cattle? I hope it's better than it is in humans, because although that experience is reassuring, unless there's some real active surveillance, I'm not sure that the results are really all that helpful.

DR. SLAOUI: I think your point is very relevant, and of course, the 26.5 million doses have been distributed in countries of Europe where BSE surveillance was happening at that time, and have continued to happen beyond that time, because of course, the cattle that are recipients of vaccine between 1988 and 1990 have continued to live over the years beyond that; and 2.5 million doses were distributed in the U.K. during which time at that period surveillance was certainly very maximum.

Not a single case has been associated with vaccination. There is a publication on association between vaccination and BSE in bovine in the U.K.

CHAIRMAN BROWN: That would be an interesting observation to make in the U.K. Can you tell me, for example, in a country with as much BSE as the U.K., that you can actually tell us that not a single cow died of BSE that had been vaccinated?

DR. SLAOUI: No. I mean, again this is statistics, but I think Dr. Ray Bradley said that there was about 1300 cases of BSE reported over the years outside of the U.K. and, if I believe, over 100,000 cases reported in the U.K. over that period.

So that gives an order of magnitude. Now can we go back and trace every single cow that have

been receiving of those 26.5 million doses of vaccine? The answer is no, because nothing was designed in that regard. But the size of that experiment is, of course, outstanding in comparison to any experiments you could do in real life.

CHAIRMAN BROWN: I think you would have to do a little data analysis. I mean, you're assuming that, for us to buy that wholesale, it would mean -- it would exclude the possibility that only, say, a small portion of the doses might have, in fact, contained an infectious dose. So that this spread, this difference -- Unless you could show that there was a clear difference between unvaccinated and vaccinated BSE cattle that died, I don't see that that's useful.

DR. SLAOUI: Well, epidemics of BSE outside of the U.K. --

CHAIRMAN BROWN: Outside of the U.K. is a different matter.

DR. SLAOUI: Right.

CHAIRMAN BROWN: But you were saying in the U.K. as well.

DR. SLAOUI: No, I'm sorry. 26.5 million doses were distributed outside of the U.K.

DR. ASHER How many lived past five years?

DR. SLAOUI: Unknown, but I think the comment -- The comment is as many as in natural bovine industry keeping animals out there, immunizing them, and some of them reaching the age at which they manifest BSE clinical disease. The sheer numbers should allow for, you know, a normal distribution.

CHAIRMAN BROWN: Go ahead.

DR. BURKE: I think this line of reasoning is actually excellent. Tt's one of the few places that we may be able to get some data without the issue of the host species barrier that may be clouding a lot of our interpretations.

You don't need to focus on the U.K. You should focus on the United States --

CHAIRMAN BROWN: Oh, exactly. I mean, U.K. is off limits, but other European countries.

DR. BURKE: Where it has not been seen. If we find that there have been millions and millions of doses of vaccines that have been prepared with fetal calf serum derived from the U.K. and used in these countries which have yet to recognize a single case of BSE in the animal population, that would, I think -- I would find that very useful as a reassuring step.

CHAIRMAN BROWN: Yes, I agree.

DR. BOLTON: But I want to get on record David Asher's point, and that is how many of those animals lived beyond five years. If we had that information, then we would really have something that was meaningful. I would recommend to the FDA that there be a specific effort to pull that data together, if possible. I think that would be helpful.

CHAIRMAN BROWN: Do you know if any of the vaccine went to really BSE-free countries like Australia and, I think it's fair to say, the USA?

DR. SLAOUI: I would like to say that we have shared with the agency this information that we are compiling and continue to compile, but you understand, for practical reasons, our company is no more having its animal health as part of SmithKline Beecham. It's been merged with another company, and finding back all the trace information for where the vaccines actually were delivered, etcetera. But these sale of tens of millions of doses were delivered across Europe and outside for many vaccines, some of which containing up to .15 milliliters of serum that were delivered either intranasally or subcutaneously or intramuscularly in countries, I am sure, in Europe where there has been no case of endogenous BSE reported.

CHAIRMAN BROWN: There was a question again or a comment.

DR. EGAN: Yes. I would just like to have a little bit of clarification from the committee. I think I heard a lot of expression for public disclosure of the issues around all of the different vaccines, but some -- I would like to know if that is the committee's consensus.

Second, I think I heard some people favoring or suggesting "Dear Doctor" letters and others thinking that that was maybe too much overkill and to change the package insert. That's going to come up in the second question, but I think we would appreciate some clarification on that or more discussion or additional opinions.

CHAIRMAN BROWN: You want more discussion on that? Well, it seems to me, the committee is uniform in its approval of some form of notification about this issue and the concept of finite risk. I think there was no dissenting opinion.

So the question now is in what form the committee might feel that would be most appropriate, and at least two options were a package insert addition to the fine print, a "Dear Doctor" letter. What are the other options the FDA has?

DR. EGAN: Well, those, I think, are the two major ones --

CHAIRMAN BROWN: Those are the two?

DR. EGAN: -- for disclosure. The "Dear Doctor" letter is very, very public. The package enclosure is limited to those who read the package enclosure.

CHAIRMAN BROWN: To those with very good eyesight, yes. What does the committee feel in terms of a choice between these two. Yes?

DE. BELAY: I'd like to know what the vaccine manufacturers feel about the disclosure issue, if somebody would comment on that.

CHAIRMAN BROWN: I'm sorry. I didn't understand.

DR. BELAY: I would like to know what the vaccine manufacturers would say about the disclosure issue.

CHAIRMAN BROWN: Okay. Before we do that, again the FDA. The "Dear Doctor" letter has nothing to do with the manufacturers. Right? That goes -- or does it? Does the manufacturer do that or does the FDA do it or who does that?

DR. EGAN: Either one could do that.

CHAIRMAN BROWN: Either one could do that.

DR. EGAN: The manufacturer can send a letter to those who purchase the vaccine, the vaccine purchasers.

CHAIRMAN BROWN: Okay. So we would like to hear at least from both manufacturers present what their viewpoint is about either one of these two options. Who wishes to speak? Yes?

DR. SLAOUI: Moncef Slaoui, SmithKline Beecham. I think I would like to reiterate what was said a little bit earlier and take a minute to do that.

CHAIRMAN BROWN: I'm sorry. What would you like to reiterate?

DR. SLAOUI: Reiterate what was said earlier.

CHAIRMAN BROWN: By whom?

DR. SLAOUI: By Mr. Jean Stephenne from SmithKline Beecham. I think the point to be considered regarding information is again to identify what is exactly the issue and where is the issue. To what vaccine does it relate? If we speak about seeds, master seeds and working seeds, having been historically in contact with bovine derived material from the U.K., for instance, in the mid-eighties -- right? If we speak about that, that means, clearly,

there has been since, say, 1985 -- you use that number -- there has been no other contact with bovine derived material ever.

The key question becomes for every single vaccine out there -- not that one specifically or those ones that are today under discussion, but for every single vaccine out there for which the seeds, the working seeds, the master seeds, the banks, the working banks, the master banks, have been in culture.

In the mid-eighties, there is a very long risk, I think it was shown or could be shown again, of animal derived material or bovine derived materials that are involved in manufacturing of those seeds that were sourced in the mid-eighties, at time at which it is impossible to ascertain and trace and document that the bovine origin materials were not sourced from the U.K.

Because we are talking about risk factors here in the orders of the billions and the hundreds of billions or thousands of billions, the probability that those other components than fetal calf serum or feed broth coming also from bovine origin could have been, in part, sourced from the U.K. or in part processed in the manufacturing -- you know, at those manufacturer places in a place where U.K. derived

material that have been used for something else was in those same recipients.

You know, we've been discussing these things earlier. How can we be confident that those things have not happened historically? We think that it is for that reason that, if this committee and the agency opts for an information on this point, the information ought to be generic to all vaccines; because, effectively, if the issue is related to the seeds, master seeds, we cannot exclude in a sure way -- again, we are talking about remote theoretical risks. We cannot exclude in a sure way that that's not present everywhere.

That's the point we would like to make, and I think that then raises the issue about the impact on perceptions of risk and perception of safety of vaccine and uptake of vaccines and immunization strategy and the impact on public health.

We would like again to reiterate, you know, real life experiment like the bovine vaccine I discussed, all the data that have been described and that scientifically documents that there is no identifiable risk associated with this vaccine -- one should really weigh the impacts.

CHAIRMAN BROWN: Well, it seems to me that

the committee has already discounted exactly what you've said. They recognize that the risk may well be infinitesimal. My feeling was that the committee feels that, despite that -- and it's summed up by the words theoretical risk -- that they have already decided that theoretical risks deserve to be called as such and publicized in some way.

Again, the question was -- just a second, Peter. The question was: In what form should that information be conveyed? So let's move beyond your objections and say --

DR. SLAOUI: Well, I guess the comment then would be generic.

CHAIRMAN BROWN: -- if that is the committee's recommendation, what form would you prefer to see it in?

DR. SLAOUI: Well, I guess, really, the short answer then it has to be generic, because scientifically you cannot prove everything --

CHAIRMAN BROWN: Okay. I think it would be generic. I don't think it's the FDA's plan to identify vaccines A through D and leave vaccines E through Z untouched. As you say, there is a sufficient absence of information from archival vaccines so that nobody probably making a vaccine

could guaranty that there wasn't this possibility of an infinitesimal risk by exposure to something that was produced between 1980 and 1990 in Great Britain.

On the other hand, if the FDA could be completely convinced, as you point out, that there are certain brands or vaccines even within a certain company that have no possibility of ever having been exposed to bovine products, than there is no point for information to be conveyed.

Peter?

DR. LURIE: First point: Package inserts are, you know, fine as far as they go, but the vast majority of patients don't see them. So I don't think that that's going to be an adequate effort on its own.

I strongly disagree with the notion that any notification should be generic. Obviously, it's in the self-interest of a pharmaceutical manufacturer who is really worried about his or her own vaccine to make sure that everybody is equally tarred, but the fact of the matter is that, even with the very difficult risk assessments that have been necessary in BSE, people have managed to divide things up into categories.

Here there are three potential categories, those were it is known that the companies disobeyed

the guidance and obtained the materials at a point in time and from a place that was precluded by FDA. There is a second group where it's simply unknown, and that can be stated, and the third is, if there somehow is a way of convincingly stating where the entire -- where the master cell lines and the working cells come from.

It seems to me that it is wrong to go and tar everybody with the same brush, because there are some ways, however imperfect, of distinguishing between vaccines. I think that, to physicians and patients, it would be enormously helpful to know that, in fact, the vaccine that you are asking about happens to be the one with which we have greater or lesser certainty that the theoretical risk is still lower.

I can't see any reason for throwing everybody into the same pool here.

DR. SLAOUI: Well, I'd like to just make a comment and say my comments, of course, were purely scientifically driven, and I simply cannot make the difference between 18 logs and 16 logs and 15 logs. That's my comment to the experts.

DR. HUANG: And I also want to say I don't think a theoretical threat is tarring anybody, and we shouldn't be even using that term.

DR. LURIE: But the whole conversation here, all the conversation about how important vaccines are and all those presentations by Dr. Orenstein this morning are precisely aimed to point out that vaccines are important, which I agree with, because we are worried that this information is going to tar vaccines. I don't think it should. I'm with you.

I mean, I think that fundamentally there is not a substantial change in the known safety of vaccines today as opposed to yesterday. But we are worried about public perceptions here and, as long as we are, and as long as we have more rather than less information, I think we should impart it to the public.

DR. SNIDER: In terms of communicating it, I would not have an objection to a letter to physicians. But it seems to me that the communication, whatever form it takes, really needs to have the whole context. One of the important messages that needs to come out of this meeting is that we do not -- I don't believe any of us want the FDA to take action which will increase the incidence of vaccine preventable diseases in this country.

So one context, of course, is to emphasize

the importance of continuing to vaccinate children against these diseases. That includes using vaccines that are currently on the shelf while, as I hear from the manufacturers, they continue to replace products that came from areas which represent a theoretical risk with products that come from areas that do not present such a risk.

For those -- and when they can do that without having to create a whole new vaccine. For those master lots, it seems to me, the question has been raised, and something that FDA should consider would be whether they can be tested, as has been suggested, if those master lots are going to be sitting around and continue to be used for some time.

Then as has been mentioned, there should be a commitment, I think, to continuing research on the part of manufacturers and FDA and others to identify new technologies which would help reduce the risk, either those technologies that improve the assays or those technologies which might remove the infectious agent.

All of that combined into a communication, I think, would be very educational for physicians, and then would help them in trying to communicate with their patients. Obviously, the communication would

include the risk, some statements about the risk assessments that have been done.

To just have a short statement that there's a theoretical risk here without a context, I think, would be a terrible mistake.

CHAIRMAN BROWN: Coming from the floor?

DR. DeWILDER: Michael DeWilder from Aventis Pasteur. I want to address also this communication issue, but before doing that I'd like to reiterate our company commitment that we made very clear. This is to make all attempts that are technically feasible to remove materials of those type of origins, and this includes, actually, master seeds.

What I want to point out is the reason we do that is not because there is a risk associated with the use of those materials or the past use of those materials, but because we are doing it because there is nothing more important to us than the perception of vaccine safety, and indeed we refer to in Dr. Orenstein's talk and to the great catastrophe that would be linked to vaccine preventable diseases; because indeed there is no risk associated with the use of those materials, and you have the calculation that we have made, and you have the expert that you have consulted, and you have the expert that's spoken

here today. Here is a fact; that's a number, whatever they are. He's using between 10^{10} and 10^{20}, whatever, it doesn't matter, in a range which are actually equivalent to no risk.

I urge your committee and the agency to take this into consideration as they choose a way to communicate this to the community.

CHAIRMAN BROWN: Thank you. Now we have heard from both manufacturers, and we have Dr. Scott Ratzan who is a professional and an expert in the whole field of the communication of medical knowledge to the general public, who has something to say. Dr. Ratzan.

DR. RATZAN: Thank you, Dr. Brown. I do spend my life doing this type of activity, as I edit the peer review Journal of Health Communication and edited a book on the mad cow crisis, Health and the Public Good that was published in 1998 by University College, London Press and NYU Press.

I'm very interested in the sort of disconnection of what I heard of some of the data earlier today and what I'm hearing now in terms of something to communicate to the public. I heard something like one in 20 billion, and I know we are using logarithmic numbers.

One in 20 billion would be one second of my life, if I live 640 years. I mean, we are talking about some very, very low numbers that don't translate very well into the public.

What my major concern is, is what I think Dr. Modlin and Dr. Snider just said, what does this do for vaccine preventable deaths. We saw the bumps earlier in the morning in terms of the measles, in terms of what happened with over 100 deaths. As a father and a physician now, I think that we have a very conscionable task to look at how we communicate this to the public, and not jump to a conclusion of this or that.

These need to be tested. There's a science behind communication, and it makes me think of what Justice Potter Stewart said many years ago. Just because we have the right to do it doesn't mean it's the right thing to do.

I think that's where we're stepping in grounds in terms of dealing with theoretical risk here. I'm just trying to think of recent experiences. We saw what happened with thimerosal a year ago where we have four different academies now, AAFP, AAP, the CDC groups, FDA groups -- a lot of people back-peddling and saying there is no risk. It was only a

precautionary measure.

We saw 79 percent of hospitals in this country change their policies in terms of childhood immunizations because of that statement that was made. In 1996 the SEAC committee similarly met in England and made a decision that they say there may be a link. They didn't have a communication person on that committee, and the House of Lords and the other groups that have looked back on it said that it was a major issue and a major mistake that they made in how $20 billion and many lives and livelihoods were lost in terms of the U.K. and Europe and the world.

I think this is a very serious discussion that needs to be made for moving from question 1, from yes, we agree with some theoretical risk which, again one in 20 billion -- two, are we going to communicate to a public, are we going to communicate to physicians, all who interpret risk very differently.

So I really implore the committee to try to think about that, not only take a scientific approach to the communication, but really take a scientific approach to look at the evidence on what the public needs to know, what physicians need to know, what policy makers need to know, and how we can continue to make healthy public policy in this area.

So I would be happy to answer questions in this regard, but I really hope that I've been able to impart that upon the committee today.

CHAIRMAN BROWN: Thank you very much. Yes?

DR. DAUM: I'd like to make a comment and then actually ask you a question. My comment is that I am, as I've been reminded today, a person in favor of full disclosure, and I am.

So that the question then becomes how. I totally agree with your comments and approach, as my earlier comment spoke to, and I don't think, therefore, that this should be product recall, which is one of the things we were asked to comment on.

I frankly don't think, with all respect to my colleague at CDC, that there should be a letter sent out to all doctors, because that's an alarming thing to have appear in your mailbox from the Food and Drug Association of the USA.

So I would say to you -- and I also don't think you should just slip something into the fine print of the package insert without letting someone know a little stinker is there. So the question is, in your experience -- you sound like a professional in this area -- how could we approach this?

I feel the need to say something. It's theoretical. I agree with your sense of how often it's going to occur totally. What could we do? What could they do?

DR. SNIDER: This is Dixie Snider. Yeah, we can hear from him, but you made a criticism of my comment, and I just want -- I thought it might be useful to have something to go along with their U.S. Today story that they were reading. That's all. Something that's authoritative from the FDA.

CHAIRMAN BROWN: I'm glad I'm the Chairman of this committee, not this committee.

DR. RATZAN: If I could try to answer that, there is a scientific nature to how do you look at communication. You don't overreact to infinitesimal risks, and at the same time you don't under-react when there is a real risk that's involved, because that does undermine the public trust.

What I heard today were some of the steps that were being taken by some of the manufacturers, the two that presented, that they are trying to embody the public trust in terms of their processes. I think more of the open nature, even meetings like this of being able to have advisory meetings, meetings also that might have the professional associations where

you have opinion leaders who might be able to defuse the information appropriately.

A blanket communication -- We often say Marshall McCluhan, a Canadian scholar in media, said, if you try to reach everybody, you reach nobody. By doing that, it's really key in thinking about communicating with the people that need to know.

Ninety million Americans are either marginally or low literate, meaning they can't understand a bus map or can't understand a bus schedule or locate their intersection on a map. We can't communicate with the same message to them that we might communicate to people who are making vaccine decisions at the state or county or other levels.

So I'm answering in a circuitous way, because I think we've heard some of the right steps being taken today, the open hearing, some of the voluntary efforts that are being done in good faith by the manufacturers, and some of the other ways that continue to monitor the open disclosure. I think the surveillance systems that we've put in place not only here in the United States but now abroad in looking at BSE and looking at the CJD that we heard from CDC and others where the numbers are.

So I would say, by all means, keep the

surveillance. Keep the voluntary efforts. Continue to focus upon the science, and communicate that appropriately on, whether it's a quarterly basis, or use the different channels, the Institute of Medicine channels that are out there.

I think there's a variety of different ways to do it, such as these expert committees as well. So, thank you.

CHAIRMAN BROWN: Thank you very much. Yes?

MS. FISHER: You may not want to communicate this theoretical risk to the public, but that doesn't mean it's the right thing to do. I think that part of what the National Childhood Injury Act of 1986 was all about, the safety provisions, was communicating risk to parents before they get their children vaccinated.

I think that, you know, the FDA's charge is to ensure the purity and potency of vaccines. It seems to me that the least that we can do at this juncture when we know something is to let the people know we know, rather than keeping it from them.

CHAIRMAN BROWN: Hold on, Dave. Shirley?

MS. WALKER: There's an old German proverb, "Don't point the devil on the wall;

otherwise, he will jump off." I think the devil has already jumped off.

The inserts in the packets for pharmaceuticals are great. Notification to the doctor is great. But I represent something like 79,000 mothers who have children in Dallas County who we actively promote to get vaccinated.

So Monday morning when I go back to work, I'm going to have to tell someone, a percentage of these young mothers, that, hey, your child is at risk for whatever that minute amount is for CJD. So what do we do at this particular point? Do we remain mute and say nothing or do we promote and give some type of information?

So I am saying to FDA that we do need some kind of general information that we can impart to our constituents.

CHAIRMAN BROWN: Thank you. I'm going to ask for just a couple of more comments in this discussion, and then in the event that a number of people on the committee may have to leave, there are two or three very specific questions that the FDA would like some discussion on, and I want to move to them. We've touched on some of them already, but if there's anything more to say on this -- Yes, go ahead.

DR. STEPHENS: I guess I'm really concerned that this discussion is kind of spinning out of control in terms of the risk. I must agree with the consumer advocate who spoke a minute ago --

CHAIRMAN BROWN: Dr. Ratzan.

DR. STEPHENS: -- that, you know, this is -- We are at some -- We have a duty, in my view, to protect the vaccine system in this country. I think that this discussion has gotten to the point of at least suggesting that we believe that this is a significant problem. The data suggests that the risk is in the billions, that there have not -- there's not been a single case of new variant CJD in this country, despite the use of vaccines that have been manufactured in this way for years.

So I think the issue is we need public disclosure. That's not the question. I think we all are in agreement on this committee, but I think to emphasize this point where you're concerned about going back to your group of mothers and saying there's a risk -- I think that's something we don't want to send. That's a message we do not want to send.

CHAIRMAN BROWN: I opened this whole seminar with the notion that we're starting from a very, very small amount of infectivity, if there is

any, and the corresponding risk was equally very, very small, if there is any, and that there is a tradeoff between, as several people have said, a theoretical risk and a real risk, which would be discrediting in some way vaccines or causing vaccine shortages or difficulties or refusal to get vaccines.

In other words, this is the tradeoff. Right at the outset, this was the scene that I hoped to set. But you're right. All of our committee discussion meetings tend to spin out of control at about this time of the afternoon, and sometimes it's in one direction, and sometimes it's in another direction.

I think the word risk has enlarged as the afternoon has progressed, and maybe we should shrink it down a little bit and get a little better perspective or a little different perspective. So I tend to agree with you. Let me --

DR. BOLTON: Paul, can I get in my comment?

CHAIRMAN BROWN: I'm sorry? Go ahead. I'm sorry, Dave.

DR. BOLTON: I agree that it wold be important to communicate known risks or even good estimates of risk to the public, but I'm not sure what

that estimate would be at this point. I don't think that we really have enough information to communicate to the public and have it be meaningful and not simply scare people away.

I can't imagine the negative impact on the vaccine program in this country if parents started thinking that, if I vaccinate my child, he or she may come down with new variant CJD.

To me, the other way that we communicate is by action. It seems to me that there are actions that can be taken in terms of looking at the process of vaccine manufacture and where the real -- the greatest of the theoretical risks are. It seems to me that the viral/bacterial master seeds are really at the very lowest end, as are the master cell banks, and also trying to change those creates the biggest problem.

From that point on, from the working seeds on down through production, I think that the manufacturers have issues that they can address in terms of removing the use of at-risk bovine materials from that point on.

I guess my question to anybody at the FDA is: Are at-risk bovine materials currently in use at the -- certainly from the production step on, and even

at the production of the working seeds and working cell lines, are they in use now, and how long before they will be phased out?

CHAIRMAN BROWN: I guess what you're -- to add to that, are the sources of anything currently coming from BSE designated countries?

DR. STEPHENS: When I say at risk, I really mean those bovine materials are coming from Europe or at-risk countries.

CHAIRMAN BROWN: Right. Does the FDA -- You might be better off --

DR. EGAN: As I mentioned in my opening talk, for some bacterial vaccines there was bovine derived fermentation media where that skeletal muscle and pancreas derived from several European countries. I think it was Germany, Denmark, Poland, the Netherlands.

CHAIRMAN BROWN: Right. So they are currently in use in this country.

DR. EGAN: They have all agreed to -- That will be changed, but as I mentioned, by the time -- You know, they've gotten new sources, but that comes into new vaccines -- What?

DR. BOLTON: Is that the only material that's now sourced from at-risk countries?

DR. EGAN: That's used in the production. I think I also mentioned hemin. I think that was it, but I'd have to go back to it.

DR. BOLTON: So I guess my recommendation would be that the FDA work with the manufacturers to set a definite timeline to phase out all those materials. In terms of the master virus seeds and the bacterial stocks and the master cell lines, I think that the risk is so small as to be really counterproductive to try to change those, because the risk of changing the product by changing those is much, much greater than any risk that there would be from proceeding.

CHAIRMAN BROWN: One of the questions that the FDA specifically wanted some judgment on was: Is it necessary to re-derive bacterial master seeds? I mean, I'm getting the sense -- Every time I get the sense of something, the sense changes. You know, we had a consensus about informed consent, and now we have a consensus about not smother it, but be awfully, awfully, awfully careful.

Now I thought we had pretty much decided that, at least for current products, that it will not be necessary to re-derive bacterial master seeds. That was my sense. Dr. Huang?

DR. HUANG: I completely agree. I think that the derivation of new master seed stocks would be more dangerous than this perceived danger that we are facing now.

CHAIRMAN BROWN: Does anybody -- As I asked before, does anybody differ from that opinion? All right. We have answered one definitive question that the FDA wanted to asked.

They also want an answer to a question I think should be very easy to answer. That is: Is 1980, form all that you have heard, an appropriate cutoff date before which one need not worry about anything in terms of sourcing of the products we are talking about?

We always worry about something, but 1980 -- is that an appropriate date before which not to be concerned? That's a pretty focused question. Is there anybody that feels that one should be concerned about products produced before 1980 from anywhere? Yes?

DR. ROOS: I think 1980 sounds like a good year, Paul, and with respect to our blood donation pool in the United States, we were concerned about BSE and started with 1980.

CHAIRMAN BROWN: It has the merit of

consistency as well. All right. That's two questions.

The third question they were concerned about was: Do we think that the small amount of fetal calf serum from the U.K. around 1985 used in the production of master cell banks constitutes a negligible or -- well, the phrase was "a negligible or a significant risk"? Again, a question about fetal calf serum, sourced from the U.K. in the middle of the 1980s, use in the production of master cell banks constitutes any kind of significant risk? Yes?

DR. CLIVER: May I start by saying negligible. We'll see if anybody disagrees.

CHAIRMAN BROWN: Do I hear significant? Negligible?

DR. BOLTON: I agree that it's negligible.

CHAIRMAN BROWN: Okay. Any differing opinion that fetal calf serum used for the production -- just for this specific purpose, used in the production of master cell banks? Well, that answers the three questions that you most wanted some judgment on. Dr. Ewenstein?

DR. EWENSTEIN: There was also the question about products that are still under investigation. I think, you know, we should address

that. I think one of the comments before was, I think, right on the point. That is that it's different if you have a licensed drug or product that has, therefore, documented benefit versus recruited volunteers.

I think we should think about what we should answer for number 3. I think that it's appropriate to include again, with the correct caveat, about theoretical and negligibly small risk in a consent form. but I certainly wouldn't like to see all clinical trials stopped of such vaccines.

CHAIRMAN BROWN: Yes. This is the idea about an investigational drugs. We haven't touched on that, and we might just continue that discussion a bit. Peter?

DR. LURIE: Yes. I think Dr. Ewenstein is right, if I understood him correctly. I think that it is indeed a different situation. For one thing, not only is the benefit of the vaccine unknown, but for another, one actually does know the name of the patients, and one is personal contact with those patients on a semi-regular basis.

I think that the ethical responsibility toward those people is quite different than is owed to the population at large. In any event, there is

simply no tracking, as far as I know, on the national level of exactly who receives what lot of what vaccine.

So I think it is distinguishable, and I think that personal notification is the way to go in the proper context.

CHAIRMAN BROWN: Let me ask a question of the people, especially, on the Vaccine side. In trials of vaccines, what kinds of risks are real? We're talking about a theoretical risk and notification. What kinds of risks in a vaccine trial actually happen? Anybody know?

I mean, it's nice to compare this theoretical risk against something that's a real risk.

DR. STEPHENS: Well, you certainly have risks of the local reactions to the vaccine. You have the intra-susception story with the rotaviruses as an example of a risk that did occur.

There are clear risks associated in a clinical trial with a vaccine.

CHAIRMAN BROWN: Or you could have, for example, an ampule or a batch that was contaminated with bacteria. I mean, that happens, certainly in -- not necessarily in vaccines, but in drugs and media.

DR. STEPHENS: That's less likely, but

yes. I mean, there are a variety, and anyone participating in the clinical trial understands that there are risks. Some of them are known; some of them are not known.

CHAIRMAN BROWN: I'm sorry? Some of them are?

DR. STEPHENS: Some of them are known; some of them are not known with any kind of IND.

CHAIRMAN BROWN: Would it be a problem for this additional theoretical risk information to be tacked on? I assume, when they have informed consent -- I mean, I can tell you a story about informed consent that is very funny, but I won't.

Informed consent is almost always signed by volunteers, no matter what it says, and I assume that the addition of a theoretical risk of this nature added to an informed consent would not be a great difficulty, if it were properly communicated, properly worded.

DR. FERRIERI: Well, don't underestimate the impact of having additional material in informed consent. It adds a huge, huge amount of time to the explanations, and the more indefinite the risk is, the harder it is to communicate, in my opinion.

CHAIRMAN BROWN: Would it be fair to say

that, if it turns out that the FDA chooses in some way to inform -- to get this information across to the recipients or at least the givers of vaccines to the recipients in the general public, if that decision is made, then consistency dictates that something also be said to recipients of investigational drugs.

DR. FERRIERI: Absolutely.

DR. STEPHENS: In consent forms, you try to list all of the things that you think might occur, and this could be one of those theoretical possibilities that would occur. So I think that that would be appropriate.

Again, going back to the emphasis, we are talking about a theoretical, in the billions risk in this particular setting.

CHAIRMAN BROWN: The story I was going to tell you: I had a tooth pulled many years ago by the Navy, and they had a consent form at the Navy hospital which listed in increasing order of seriousness the various complications, and the next to last line was death. The last line was "Other."

DR. FERRIERI: I'd like to revisit the issue of the communication and propose one possible avenue as a preliminary. That would be for FDA to write a brief one-page sort of "for your information

based on our meeting" that would be submitted to JAMA. It reaches so many physicians, and it might defuse the issue of what they may read in the newspaper; and depending on what's on Web sites, parents will start coming in and asking questions before physicians will even have been aware of the issue perhaps.

Dr. DiAngelis, the editor, might be very interested in some sort of statement "for your information" as the thrust of it.

CHAIRMAN BROWN: I think that's a crackerjack idea. The JAMA -- After all, vaccination reaches the general public like no other form of therapy, and the JAMA probably has the widest distribution to that part of the medical community involved in vaccination.

So what does the FDA think about that? I see a head nodding. Good.

DR. EGAN: I think it's a good option.

CHAIRMAN BROWN: Peter?

DR. LURIE: I guess the day is getting late. I can feel my caffeine levels dropping. I guess it makes me want to think about prevention in a general way, and particularly how we can prevent ourselves from being in this particular situation that this committee has found itself today.

This really is an unnecessary situation we're in. In that sense, this meeting is unnecessary. And it's unnecessary, because there was inaction or improper action by two groups of players here.

The first is the FDA which threatened to produce a regulation, but instead provided a guidance which then provided them with no ability to enforce, if it were necessary.

I think the lesson here is for all the claims by some of the manufacturers who are here that they are doing the best they can to get rid of the BSE country sources for these vaccines, there are many vaccine manufacturers who aren't here today.

So if we are to prevent this from happening again, the first thing that needs to happen is we need to regulate, not provide guidances; because guidances can, and in this case were, ignored by the industry.

The industry takes the other responsibility for this. We have experts at the FDA who came to the conclusion that the right approach to this was to source the materials from non-BSE countries, and the industry has recklessly, in my view, decided simply to ignore that.

Had either of those two things been in

place, we wouldn't be here today, and all of this discussion would have been unnecessary.

CHAIRMAN BROWN: Ms. Fisher?

MS. FISHER: I absolutely agree with you, and I think that the reason we are meeting today is exactly what you said. Therefore, I think the FDA has the duty to ask the vaccine manufacturers involved to put it in the product manufacturer insert. At the very least, that should be done.

I wasn't saying it should be, you know, put out in a physician's statement or a letter to physicians, but it should be in the product manufacturer insert.

DR. BOLTON: Paul, I have a question, I guess, for the vaccine group. That is, to put this in perspective, as what Paul had mentioned earlier, other real vaccine risks -- for example, the switch from the active attenuated polio vaccine to the inactivated vaccine was prompted by cases of paralytic polio.

How long did it take that action to occur from the time that it was first recognized to the time the switch was made?

CHAIRMAN BROWN: Can anybody in the audience answer that question?

DR. FERRIERI: Well, there is someone in

the audience who could answer it best, and that's Dr. Katz.

CHAIRMAN BROWN: Dr. Katz.

DR. KATZ: Vaccine associated paralytic disease was probably first recognized in the late 1960s, but what you were doing was calculating a risk-benefit over the years of an effect that was about one in a million versus thousands of cases of polio. It wasn't until polio was controlled in this country that the issue became crystallized as when was it appropriate to take the risk of switching to an injectable vaccine which was less acceptable to the public in many ways, more difficult to administer, less available, contrary to the recommendations of the World Health Organization.

It took a good number of years from meetings in the 1980s until polio was declared eliminated from the Western Hemisphere in 1994 to convince the recommending committees to make that change.

DR. BOLTON: And I guess that, I think, emphasizes my point. That is that, in a real risk situation, it even can take years to take an action versus here where we have a very less than negligible theoretical risk. I don't think we should feel bad

about moving slowly, and I think it's inappropriate, really, to talk about inappropriate actions on the part of you, the FDA, or the vaccine manufacturers.

I think people are moving at an appropriate speed and contemplating and thinking about these issues very carefully.

CHAIRMAN BROWN: Thank you. I will ask if anyone on either committee or the joint committee has anything that they have not said that they definitely want recorded as a public statement before I conclude the day's proceedings.

I think the FDA was very astute not to ask this committee to vote on any of the issues, but I think the FDA has received a great deal of pros and cons and discussion, and I think the meeting was very worthwhile, and thank you all for coming.

(Whereupon, the foregoing matter went off the record at 5:13 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: JOINT MEETING

Before: TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE AND VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

Date: JULY 27, 2000

Place: BETHESDA, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis