adenovirus virions or virions of any virus vector that's being used.

The second case is particularly worrisome in a sense because, as compared to DNA that's floating around free, because you're giving that DNA a very efficient means not only of getting into the cell, but getting into the nucleus of the cell, and so I think that's something that ought to be looked at, at least looked at experimentally to see what the issues really are.

ACTING CHAIRMAN DAUM: Thank you.

I can reassure you that every word is being recorded, and from what I've seen of my E-mail since I've chaired this Committee, read very carefully.

Dr. Moulton and then Dr. Aguilar-Cordova.

DR. MOULTON: Okay. Just a few points. One is I don't think I've heard anyone commend the risk analysis that was done for TSE/BSE, and actually I was pretty well impressed by that. It was basically a combination of prevalence and dilutional calculations, and you know, if I had a one in 1,000 risk of getting HIV next year, I wouldn't hesitate to line up for a vaccine based on this product.

So that didn't bother me. I guess also

because I'm not from the U.K.

But on the other hand, I think I did hear a lot of people saying that we do need more data for the oncogenicity question because those calculations are basically a linear extrapolation from a dozen unfortunate chickens, and we do need some more information there.

And the other thing is that a calculated risk is not the same thing as a managed risk, and it would be good to make sure that we have a good plan down the line for how to manage these risks because at the end of the day, we're not going to know what they are very closely, and there are things we can do to manage them, and these include longer term follow-up of patients who are in Phase 1 and Phase 2 trials, as well as enhanced surveillance methods and efforts at the point of introducing vaccines into the population.

ACTING CHAIRMAN DAUM: Thank you very kindly.

Dr. Aguilar-Cordova.

DR. AGUILAR-CORDOVA: Yes. An issue that hasn't been brought up and trying to think of novel --

ACTING CHAIRMAN DAUM: Thank you.

DR. AGUILAR-CORDOVA: -- this is something that we've looked at in the gene therapy and discussed

at RAC quite often, and that is the shedding of vectors, and of course, we're looking at it in a small population, but if one thinks about a larger population, there will be many of those that would receive the vaccine that may have active adenoviral infection or get active adenoviral infections through that period and then co-package or carry the new vaccine and shed that to the environment in general.

That may be a positive or it may be a negative. I'm just putting it out there as a risk factor that is certainly possible.

With regard to packaging of cellular genes, that is not a very efficient issue with adenoviruses.

ACTING CHAIRMAN DAUM: How efficient do you need to be though? That's the question.

Thank you very kindly.

Dr. Cook and then Dr. Priola, Dr. Kohl, Dr. Faggett.

DR. COOK: I just want to respond to Ms. Fisher's point about SV40 being cultured from a variety of different types of tumors. It's probably good to set the record straight and say that wasn't the case. In fact, SV40 in most of these studies has been detected only by fairly high PCR cycling, and so

it's sequenced detection, not viral infection that's being detected in these tumors.

ACTING CHAIRMAN DAUM: Thank you for clarifying, Dr. Cook.

Dr. Priola, please.

DR. PRIOLA: Yeah, I want to bring back up one issue that struck me this morning from Dr. Hughes' talk, and that is how, of course, we all know that passage of tissue culture cells over time can change the properties of the cell, and that the discussion, if I've been following it correctly anyway, seems to be concentrated on approval or trying to set up tests that could be done to eventually get these cells approved for production of vaccines.

But if that approval occurs, is it worthwhile to consider occasional follow-up testing, not perhaps as rigorous as the initial testing, but occasional follow-up testing to insure that the properties of the cells that had been characterized in the beginning are maintained?

ACTING CHAIRMAN DAUM: Does someone want to address that? Dr. Golding?

DR. GOLDING: Yeah, I think one of the procedures that are in place is to require the sponsor to establish master cell bank at the very early stages

of passages, and therefore, all of the characterizations that are done on that master cell bank should remain in place, and only this master cell bank is used for future production of new lots rather than the concept of just continue to passage the cell.

If a new master cell bank has to be established, then, of course, all of the tests have to be done again.

DR. PRIOLA: Well, okay. Then so just as an ignorant question on my part because I don't know much about this, when cells are pulled out for vaccine production, how long would a cell line such as these PER.C6 cells be maintained once it's pulled from the master bank to produce the vaccine?

So I'm assuming that it would be for a very limited amount of time.

DR. GOLDING: That's correct. You have a master cell bank. Then you have working cell banks which are used for expansion for production of a given lot, and a lot of the testings are done on them as well, and that's the end, and then the next lot has to start again from another --

DR. PRIOLA: Thank you.

ACTING CHAIRMAN DAUM: Thank you very much.

Dr. Faggett. Did you not speak yet? I'm sorry.

DR. FAGGETT: Dr. Kohl is first.

ACTING CHAIRMAN DAUM: I apologize. I crossed his name off by accident.

DR. KOHL: No respect.

(Laughter.)

ACTING CHAIRMAN DAUM: On the contrary.

DR. KOHL: Thanks, Bob.

One of the early things we heard about the PER.C6 cells being described was their construction to avoid recombination, and I've been around long enough to have some skepticism that that's another one of those 100 percent things.

We haven't talked about that much. What do the experts feel about how, you know, fail safe these cells are in terms of not being able to recombine?

ACTING CHAIRMAN DAUM: Dr. van der Eb?

DR. VAN DER EB: You can never exclude formation of RCA in any cell type. There is always the chance that non-homologous recombination takes place. So you can never exclude that. It is only far less likely. That is all I think we can say.

ACTING CHAIRMAN DAUM: That makes it a

simple piece of this puzzle, doesn't it?

Dr. Faggett, please.

DR. FAGGETT: Thanks, Bob.

Back to Dr. Hughes' point about the assays that are going to be available. They mentioned that there's a lot of experimental assays being looked at. What's being done to really accelerate FDA approval of those kind of assays?

So that I think that's a critical part of assuring safety issues. That's my additional concern.

ACTING CHAIRMAN DAUM: Anyone want to comment from the agency on that?

DR. KRAUSE: Yeah, I'm not sure that specific assays that address scientific points require -- maybe I'm saying the wrong thing -- but I don't think they require FDA approval. FDA approves products that are used in diagnostics of people, but if there is an assay which will have value in assessing a cell bank or a cell substrate or a vaccine, that assay can be done without some kind of an independent approval process of that assay.

DR. FAGGETT: Well, I think my real question is what is being done to really accelerate availability of those assays. I think I did misspeak. I'm speaking specifically experimentally.

DR. KRAUSE: You know, I think there are several approaches. One of them, of course, is to try and do research at FDA which improves people's familiarity with these kinds of assays so that they understand them and how they behave.

Another one is when products come in for discussion, to discuss the possibility of doing these kinds of assays with the manufacturers and the sponsors, and if it appears as though the assays are going to be of some value, to either use some data generated at FDA to encourage them to do it or perhaps to make those kinds of encouragements even without internal data.

But if an assay looks as though it's promising and has a real chance to answer a question that is important in a regulatory sense in a reasonable amount of time, then we're not precluded from asking for that to be used.

ACTING CHAIRMAN DAUM: Thank you very kindly.

I think we may be sort of partied out.

(Laughter.)

ACTING CHAIRMAN DAUM: I would like to make a couple of comments perhaps before we close. One of them is that I think that judged by the

Committee's comments and consultants' comments this afternoon, that we're generally very impressed with the effort that the agency has made to deal with the issues that are on the slide.

There's lots of unknown questions, and there's lots of unknown issues, but one doesn't get the feeling that there's lots of unaddressed issues, and I think the agency is to be commended for taking an aggressive and thorough stance toward beginning to look into this very difficult issue.

I think one of the things that we did talk about today several times in addition to lots of fine tuning of efforts underway is the idea of more mathematical modeling and risk assessment, if those are the correct terms to use, Drs. Goldberg and Moulton, to get some sense of what kinds of risk we're talking about as quantified, although as Dr. Kohl correctly points out, we don't want to take them too seriously or put over emphasis on that one approach.

I think one of the background issues that was hinted at several times was that the diseases that this research is intended to culminate in and prevent are absolutely devastating and are killing many millions of people all over the world, and that's why at first glance one might throw up their hands and

say, "Well, look. We just don't want to take any risk and we're going to just stop this until we know everything."

But then the disease commands us, I think, to continue to develop this, and I'm drawn to the example of polio in sort of closing, which people in the room know a lot more about than I do, particularly Dr. Katz.

But when first vaccines were licensed against polio, there were 50,000 children a year being paralyzed in the United States. And an admittedly imperfect vaccine was put out that itself caused polio, very rarely, and produced a lot level residuum of disease in this country.

At that time I think that even if this Committee were today addressing that very issue, that that tradeoff would be worth it. That 50,000 children not being paralyzed every year would be worth an imperfect vaccine that we didn't know everything about.

Naturally once the disease was virtually eradicated and there were no cases occurring from wild type virus anymore, then we had a different situation where we had to readdress that very issue.

But here we have a disease that is

epidemic in many parts of the world, and we have vaccines that show some promise in helping to deal with that enormous disease burden, and I'm very impressed with the effort gathered in this room today to begin to quantify and address and conduct research into making those issues as minimal as they possibly can be.

Are there any other comments from Committee or consultants?

I think the Committee has been wonderfully interactive today and up front with comments. Our consultants have been fantastic in terms of getting issues raised and discussed.

Speak now.

(No response.)

ACTING CHAIRMAN DAUM: We're adjourned.

Thank you very much.

(Whereupon, at 5:17 p.m., the meeting in the above entitled matter was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: DHHS/FDA/PHS/CBER

Date: May 16, 2001

Place: Gaithersburg, MD

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