Dr. Gellin.

DR. GELLIN: I have no additional comments on that.

CHAIRMAN DAUM: Thank you.

Dr. Steinhoff, where are you? Gone, not forgotten.

Dr. Myers.

DR. MYERS: I think it's an appropriate study.

CHAIRMAN DAUM: Dr. Overturf is gone.

Dr. Diaz has spoken. Do you want to speak again to this?

DR. DIAZ: I haven't really weighed in on this particular issue.

CHAIRMAN DAUM: Weigh in, please.

DR. DIAZ: I would consider doing essentially what they have described, although I'm not really clear as to what the appropriate study would be. Something along these lines, and perhaps assuring that there is no other adverse events that are not mentioned here that would be considered potential serious adverse events. Obviously it goes without saying.

CHAIRMAN DAUM: Thank you.

Dr. Markovitz.

DR. MARKOVITZ: I have nothing to add.

CHAIRMAN DAUM: Dr. Parsonnet?

DR. PARSONNET: I have nothing to add, but could I address the next question because I also have to leave?

CHAIRMAN DAUM: Yes.

DR. PARSONNET: For the next question which is on post marketing trials, I'd like to see more comparative studies with the inactivated vaccine and also more data specifically on efficacy in the age groups that we have been talking about.

CHAIRMAN DAUM: Thank you very much, and please travel safely.

Ms. Fisher.

MS. FISHER: Well, it sounds like we need to know more about the biological mechanisms for vaccine induced immunity and the correlates for immunity, and so I haven't got a clue as to what the endpoints would need to be.

CHAIRMAN DAUM: Okay. Thank you, Ms. Fisher.

Dr. Goldberg?

DR. GOLDBERG: I think what's being proposed is probably fine, assuming that all the other adverse events are recorded. My only question

is if you do this shortly before you're going to develop and produce the vaccine for that year, what does this do to the production timetable. I mean if you had a result that you now had to deal with, when do you do this?

DR. YOUNG: Dr. Daum, would you like me to comment on that?

CHAIRMAN DAUM: I believe I would.

DR. YOUNG: Thank you.

Basically what we do is once we make the MVS, we expand that one more passage and make a clinical trial lot as we move into production. So the clinical trial lot is made in parallel with production of the commercial material, if you will, and while we're making commercial material, we do the safety study at risk as a release test.

DR. GOLDBERG: That was what I was wondering, but it could theoretically impact your production for the year; is that right?

DR. YOUNG: We certainly don't wait for the results before we start production.

DR. GOLDBERG: Yeah, but supposing you're at risk.

DR. YOUNG: Oh, absolutely. If we have a hot strain that has developed, we're -- I don't

want to use "dead in the water." That's not a good term to use around you all.

CHAIRMAN DAUM: We can't handle it.

(Laughter.)

CHAIRMAN DAUM: Dr. Steinhoff, did you want to comment on issues related to discussion point three?

Nothing to add. So I'm the last person, and I would like to see. I think the FDA proposed plan is sound. I will make my pitch for annual monitoring of efficacy once the vaccine is deployed, and one idea I had about how to do that, which would obviously take a lot more thought than my comment here, is in areas where there's influenza surveillance to perhaps develop a case control technique to assess efficacy of the vaccine each year.

I find myself wanting to know that about influenza vaccines of any sort and would love to see data about that.

Also, if I hear the drum beats correctly, we're moving more and more toward immunizing children not in the near future, but certainly in the future is my suspicion, and if that's so, the plan to do testing on adults alone

that was proposed won't be enough, and there will have to be children included in that annual evaluation as well.

And, Michael, before we leave discussion point three, would you like to give us industry perspective?

DR. DECKER: Very briefly.

CHAIRMAN DAUM: Thank you.

DR. DECKER: Concur with the proposal, and with respect to the questions about additional data, I think it has become clear now that this test can only be -- it's the last safety check for a hot lot. If you failed the test, which hopefully no one ever will, you've lost your production. You may not even be able to go back and make any more in time.

The thought that you're going to get data out of this then allows you to adjust what you're doing that year is simply not supported. You can't do it.

CHAIRMAN DAUM: Thank you very much.

We move on to discussion point four, but I'd like to preempt the discussion by at least pointing out that I believe that a great majority of the things that we'd like to see done have been addressed, but we will survey the committee to make

sure there's nothing else that people want to say.

Of course, discussion point four deals with if the data are adequate to support safety and efficacy, to discuss what additional information, if any, should be requested from post marketing studies.

One point to keep in mind as we go around on this is that if you believed that the data were not adequate, then perhaps this question is moot, at least as I understand how it's written. FDA people agree?

DR. MINK: Actually, yes, I agree. Most of the deficiencies from the committee members who voted no they stated at the time they voted.

CHAIRMAN DAUM: I believe so. So we'll just run around quickly and make sure there's no other comments, and then we can consider adjournment.

Dr. Stephens, anything else?

DR. STEPHENS: Well, I want to be sure the list is full and long because I think there is a long list of post marketing issues that need to be addressed.

The revaccination safety issue, for example, and efficacy issue I think is one that

needs to be addressed. The whole issue of asthma in children needs to be better addressed and understood because, you know, it was the clear hope that this vaccine would be used in younger children, and I don't understand the asthma issue all that well, nor do I understand it in influenza in general. It needs to be addressed.

The viral shedding and reassortment issue, I think, is still out there and needs post marketing assessment. The transmission high risk individuals, we've discussed that today. It's still an issue that's on the table and needs additional post marketing studies.

Dr. Parsonnet mentioned the issue of comparative studies with the inactivated influenza vaccine, and then the age group issues that we've already discussed in depth.

I would urge also because I think it would really help for future vaccines of this nature to understand the immune correlate of protection. We simply do not understand that for this vaccine. We have just recently been told that antibody is a worthless guide for this particular vaccine, but we need to understand how this vaccine works in terms of future vaccines.

CHAIRMAN DAUM: Thank you.

You'll be pleased to know that those of us that were keeping a list of things that were made before had a pretty good cross-reference with your list, but it doesn't hurt to review, and almost all of those things are actually in the record, which is good, and the agency, I think, has heard, but let's make sure.

Dr. Katz?

DR. KATZ: It seems to me I don't know if it fits under the purview of question four, but what I would like to see is a study of the vaccine used in high risk individuals. We heard a little bit about HIV infected individuals, but I think there are many other groups whom we list as high risk.

I don't know if that's something the company is interested in doing, if it's something that FDA would endorse with an IND, but one way or another I think that questions needs to be answered.

CHAIRMAN DAUM: For several reasons actually.

Dr. Edwards?

DR. EDWARDS: I think that as a pediatrician the delivery of inactivated vaccines

currently even to our high risk groups is not very good. I think flu vaccine, internists do much better than pediatricians. That's probably the only vaccine, however.

But I think that the delivery system is an interesting one and does perhaps open much broader array of opportunities for young children to be immunized. So I would really urge that the additional studies on the mechanism of the reactive airway disease be done so that ultimately this vaccine might be delivered to the children that were supposed to be the target population in the beginning.

CHAIRMAN DAUM: Thank you very much Kathy.

Dr. Snider.

DR. SNIDER: Well, with regard to the reactive airways disease, I mean, I think we need to keep in mind that given the numbers, there may be problems in persons older than 60 months of age, and so we need to be attentive to that.

And also, as I mentioned earlier, I think we need to look at this issue of asthma or reactive airways disease in the larger context in terms of what might be induced by FluMist versus

what might occur as a result of natural infection and what might be prevented or not prevented by the inactivated vaccine.

And so I think those are interesting questions. I think it has probably already been mentioned that we need to continue to look at the transmission issues, both the inadvertent and otherwise. The reassortment issue obviously needs to continue to be monitored.

Revaccination has been mentioned. Risk groups, safety and efficacy has been mentioned. The age group is not included, may or may not have been mentioned, but I hope they're on your list of things that should be looked at.

And immune correlates have been mentioned. Operational issues also would be of interest, although I'm not sure they're necessarily post marketing studies in terms of things you would lay on the manufacturer, but in the broader context if you interpret post marketing as things that might be done in the context of after licensure by someone, the thing that was mentioned earlier in terms of who will administer this vaccine and can it be self-administered or would it be administered by ancillary medical personnel or pharmacists and so

forth; I think those things are interesting topics to look at down the road.

CHAIRMAN DAUM: Thank you, Dixie.

Dr. Hamilton, please.

DR. HAMILTON: I have nothing to add.

CHAIRMAN DAUM: Thank you very much.

Dr. Eickhoff.

DR. EICKHOFF: Nothing further to add.

CHAIRMAN DAUM: Dr. Cox.

DR. COX: Nor I.

CHAIRMAN DAUM: Dr. Gellin.

DR. GELLIN: I want to pick up a little bit where Dixie left off because I think the post marketing studies might depend or will depend on how this vaccine is marketed, and because it has the potential to be self-administered, you could envision how this might be something that is given as a prescription and somebody goes and gets this at a pharmacy and then does their own thing with it.

And given that, I think there may be implications for both analyses of safety and effectiveness when it's self-administered because it's not necessarily something you can do without some instruction.

CHAIRMAN DAUM: Thank you, Bruce.

Dr. Steinhoff.

DR. STEINHOFF: I just want to underline a point that's been made, to ask for additional data on high risk groups, which would also speak to the issue of transmission to that high risk group.

CHAIRMAN DAUM: Dr. Myers.

DR. MYERS: All been said.

CHAIRMAN DAUM: Dr. Diaz.

DR. DIAZ: Nothing to add.

CHAIRMAN DAUM: Dr. Markovitz.

DR. MARKOVITZ: Nothing to add.

CHAIRMAN DAUM: And Ms. Fisher.

MS. FISHER: Nothing to add except I can't imagine that we're going to have people administering this to themselves or to other people. That sounds like a nightmare, prescription for a nightmare to me.

CHAIRMAN DAUM: Thank you.

Dr. Goldberg.

DR. GOLDBERG: Nothing to add.

CHAIRMAN DAUM: And I have nothing to add. Everything has been said.

So with that, two things before we start making noise. One is for committee members. There's a van downstairs at 5:00 p.m. to go to

airports.

And, two, I want to thank the committee first, the sponsor second, and of course the agency third for a day of respectful and, I think, good scientific exchange.

Thank you. We are adjourned.

(Whereupon, at 4:42 p.m., the Advisory Committee meeting was concluded.)

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: December 17, 2002

Place: Bethesda, MD

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