FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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MEETING ON INFLUENZA VIRUS VACCINE FORMULATION FOR 2002-2003
AND CBER LABORATORY SITE VISIT FOR LHV AND LVBVD

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WEDNESDAY
MARCH 6, 2002

The Advisory Committee met in Building 29, Room 121, NIH, Bethesda, Maryland, at 12:30 p.m., Dr. Robert S. Daum, Chair, presiding.

PRESENT:

DR. ROBERT S. DAUM,
DR. ESTUARDO AGUILAR-CARDOVA
DR. PAMELA S. DIAZ
MS. BARBARA FISHER
DR. BILL FREAS
DR. BILL EGAN
DR. DAVID MARKOVITZ
DR. NEIL GOLDMAN
DR. JODY SACHS
DR. JULIE PARSONNET
DR. KAREN MIDTHUN
DR. KWANG SIK KIM
DR. LEWIS MARKOFF
DR. PETER PALESE
DR. ROLAND LEVANDOWSKI
DR. STEPHEN FEINSTONE
DR. STANLEY LEMON
DR. SAMUEL L. KATZ
DR. JERRY WEIR

OPEN

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

12:33 p.m.

DR. DAUM: We ask that all committee members identify themselves each and every time we talk because the transcriber will not recognize anyone's voice probably by sound.

We also ask the usual extension from cellular phones. Should noise occur in your office, or if you need to make noise in your office, we would appreciate if you would use the mute button on your phone. Do not place the meeting on hold because we may hear a lot of background music if you do that.

At this point I would like to welcome Jody Sachs to our committee's deliberations. I think this is her first solo meeting and she's stepping into tall shoes here replacing Jerry.

Welcome, Jody. Would you begin with your announcements?

DR. SACHS: Sure. Thank you, Dr. Daum.

Good afternoon. My name is Jody Sachs, the Executive Secretary for today's meeting of the Vaccine and Related Biological Products Advisory Committee. I would like to welcome all of you to the 90th meeting of the Advisory Committee.

There is a speaker phone for public

participation located here in Conference Room 121, in Building 29, at the NIH campus.

This afternoon's session will consist of a presentation and committee discussion that will be open to the public. We will then go to a closed session until the meeting is adjourned as described in the Federal Register notice of February 22, 2002.

Should a committee member get dropped from the teleconference line, simply call back at the 800 number which is 1-888-316-9409 and ask to be connected to the ID number 17271. The operator is under strict instructions only to connect committee members to this line. That number again is 1-888-316-9409 and the ID number again is 17271. If you have a problem while on the call, you can reach the operator by pressing *0 at anytime and she will help.

We ask that you do not place -- use your hold button because many clinical centers have background music that can be distracting to those on the call. I strongly urge everybody again to use the mute since there are many lines going and it will decrease the background sound. It will help everybody.

I would like to introduce the members of the FDA staff that are around the table this

afternoon. Let me start with Dr. Karen Midthun, Director of Office of Vaccine Research and Review, Dr. William Egan, Deputy Director, Office of Vaccine Research and Review, Dr. Norman Bailer, Associate Director for -- I'm sorry. Dr. Bailer is not present at this time. Dr. Roland Levandowski, Office of Division of Viral Products, Dr. Neil Goldman, Associate Director for Research, Office of the Center Director at CBER, Dr. Jerry Weir, Director of Division of Viral Products.

Later for Session 2 Dr. Stephen Feinstone, Chief of the Laboratory of hepatitis Viruses, and Dr. Lewis Markoff, Chief of the Laboratory of Vector-Borne Viruses, will be joining us as well as Dr. Stanley Lemon, the Site-Visit Team Chair and Professor and Chairman, Department of Microbiology and Immunology and Dean of the University of Texas Medical School.

I would also like to introduce you to Denise Royster. Denise is the Committee Management Specialist at OD SACS. I would like to personally thank Denise for competent handling of all the details to pull this meeting together. I am indebted to her.

I do ask that all their committee members identify themselves each and every time they talk. As Dr. Daum mentioned, we have a transcriber present who

will need your assistance in order to attribute all the comments to the appropriate members.

At this time I would like to read a conflict of interest statement. The following announcement addresses conflict of interest issues associated with this meeting of Vaccine and Related Biological Products Advisory Committee on March 6, 2002.

DR. SNIDER: Jody, this is Dixie Snider. You're fading in and out on us.

DR. KATZ: Sam Katz. The same thing is happening here.

DR. WHITLEY: Same in Birmingham.

DR. SACHS: I just removed the speaker phone for the moment. I'm just going to still address. You tell me while I continue if there is additional problems. Unfortunately, not everybody in this room can hear but we'll continue reading the statement and then I'll put you back on.

Based on the agenda made available, it has been determined that the committee discussions present no potential for conflict of interest. Participating in this teleconference are vaccine manufacturers. The reason for their participation is to present the industry's point of view.

The Director of the Center of Biologics, Evaluation, and Research has appointed Dr. Robert Couch, Dr. Walter Dowdle, Dr. Theodore Eickhoff, Dr. Kwang Sik Kim, Dr. Steven Kohl, Dr. Stanley Lemon, and Dr. Greg Poland, as well as Dr. Dixie Snider as temporary voting members for the committee discussions.

In the event that the discussions involve specific products or firms not on the agenda for which the FDA's participation have a financial interest, their participants are aware of a need to exclude themselves from such involvement and their exclusion will be noted for the public.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

I'm going to place you back on speaker. I'm getting a lot of background noise and all I ask is that if you're not speaking presently, use your mute button and see if we can continue.

I now at this time wish to turn over the meeting to Dr. Daum.

DR. DAUM: Thank you very much. We're not

doing absolutely perfectly in terms of clarity. I guess people are just going to have to pipe up if they can't hear well.

At this point we would like to call the roll and see who's here. I'll just go around the table, so to speak.

DR. SACHS: Dr. Daum, the sound is not coming across very loud at all.

DR. DAUM: Can you hear me reasonably well?

DR. SACHS: No. There's too much background.

DR. DECKER: Could you try using your handset instead of a speak phone, Dr. Daum?

DR. DAUM: I'm going to try that right now.

DR. SACHS: Thank you.

DR. DAUM: Hello. Is that better?

DR. DECKER: That makes you much better, Bob. This is Michael Decker and I believe I'm detecting the sound of the cell phone if anyone is on a cell phone. I believe part of the interference came on when somebody joined who isn't muted.

DR. DAUM: That could well be. I'm just not knowledgeable enough.

DR. SACHS: Okay. I would like to --

DR. DAUM: There is some buzzing that fades in and out. There it is.

DR. SACHS: If anybody is on a cell phone, could you hang up, please, and call back on another line. All those who are not speaking, just use mute and we'll see if we can proceed. Thank you.

DR. DAUM: That worked. Whoever hung up, thank you.

DR. SACHS: Thank you.

DR. DAUM: Let's go around and see who's here. Dr. Aguilar-Cordova.

DR. AGUILAR-CORDOVA: Yes, I'm here.

DR. DAUM: Welcome. Michael Decker I know is here. Pam Diaz.

DR. DIAZ: I'm here.

DR. DAUM: Welcome. Dr. Walter Faggett? Dr. Faggett, are you here?

DR. SACHS: He is here. I'm sure he's on mute.

DR. DAUM: Okay.

DR. MIDTHUN: He was the cell phone.

DR. DAUM: Dr. Griffin? Dr. Griffin? What about Dr. Goldberg?

DR. GOLDBERG: I'm here.

DR. DAUM: Dr. Katz.

DR. KATZ: Here.

DR. DAUM: Dr. Markovitz.

DR. MARKOVITZ: Here.

DR. DAUM: Welcome.

DR. MARKOVITZ: Thank you.

DR. DAUM: Dr. Overturf.

DR. OVERTURF:Here.

DR. DAUM: Dr. Palese.

DR. PALESE: Here.

DR. DAUM: Dr. Parsonnet. Dr. Parsonnet. Dr. Stephens.

DR. STEPHENS: Here.

DR. DAUM: Dr. Whitley.

DR. WHITLEY: Here.

DR. DAUM: We have three new committee members, some of you may have noticed, for this meeting. We would like to especially welcome Dr. Aguilar-Cordova, Dr. Markovitz, and Dr. Overturf. Welcome to our committee.

To go on with invited guests, consultants, and speakers. Dr. Couch, are you here?

DR. COUCH: Here.

DR. DAUM: Dr. Cox.

DR. COX: I'm here.

DR. DAUM: Dr. Diniega.

DR. DINIEGA: I'm here.

DR. DAUM: Welcome. Dr. Dowdle.

DR. DOWDLE: Here.

DR. DAUM: Dr. Eickhoff.

DR. EICKHOFF: Here.

DR. DAUM: Dr. Kim.

DR. KIM: Here.

DR. DAUM: Steve Kohl.

DR. KOHL: Good morning.

DR. DAUM: Hello. Morning in some places.

DR. KOHL: Exactly.

DR. DAUM: Dr. McInnes.

DR. SACHS: She's not here. Not present today.

DR. DAUM: I think we won't go through the FDA folks again because Jody went through that before we started.

DR. SACHS: What about Dr. Snider and Dr. Poland?

DR. DAUM: I'm obviously missing them. They are not on the sheet that I have here.

DR. POLAND: This is Dr. Poland. I'm here.

DR. DAUM: Good. And Dr. Snider?

DR. SNIDER: I'm here, Bob.

DR. DAUM: Welcome both of you. Your names are not on the list that I have and I apologize for that.

Okay. With that attendance in order, I think we're ready to move into the business of the meeting. Session 1 is an open session where we are going to continue the discussion with strain selection for influenza virus vaccine for next season. We will begin with our Dr. Levandowski who will introduce the topic in review where we left off.

DR. LEVANDOWSKI: Thanks, Dr. Daum. I would just like to make a comment, just a clarification for the rest of the remainder of the information to be presented today on the conference call.

I'm going to do a review in introduction of where we are at this point. When I'm done, then Dr. Cox and her colleagues at CDC will be able to provide some additional surveillance data.

I have some additional vaccine study information and some information about correct status of influenza virus strains and re-agents. Then Dr. Cox and her group again would be doing the options as we see them for making recommendations at this point.

If that's okay, I'll just go ahead then and start with the introduction and review. First I'll ask can everybody hear me okay?

DR. DAUM: Yes.

DR. LEVANDOWSKI: I think probably you can?

DR. SACHS: Yes.

ALL: Yes.

DR. LEVANDOWSKI: Great. So I'll just go ahead. The reason we're here today, as Dr. Daum has already mentioned, is to complete the recommendations for the composition of influenza virus vaccines that will be used in the United States during the 2002/2003 influenza season, the one that's coming up.

You'll probably all recall that on January 30th the committee met to begin making those recommendations. There was a lot of information that was available to us at that time and there was information presented on surveillance and epidemiology of influenza viruses in the United States and around the world.

Also serologic responses to current influenza vaccines and on the suitability of recent influenza viruses for use in manufacturing. After the committee heard that information in January, it

recommended that the influenza A(H1N1) component of the vaccine should remain the same as it had been which is A/New Caledonia/20/99(H1N1) strain.

Also recommended that the influenza A/H3N2 component of the vaccine should remain the same as it had been as an A/Panama/2007/99(H3N2) unless there was any new compelling information that would be accumulated between the time of that meeting and the current time that would suggest that some other strategy might be a better one.

The committee also recommended for the influenza B component of the vaccine that decision would best be deferred to accumulate some additional information. However, there was a lot of discussion about the need to change the influenza B component based on the information that we had at that time.

What stimulated the discussion on influenza B was partly the recent recognition that there have been widespread co-circulation of influenza B viruses of the two known hemagglutinin lineages that are represented by the reference strains B/Victoria/287 and B/Yamagata/1688.

Some of the points that were considered in the discussion included the fact that there was evidence of antigenic drift continuing in influenza B

viruses of both of those lineages, both of those HA lineages.

The fact that B/Victoria/287/HA lineage strains have been found outside Asia for the first time since the early 1990s. You'll recall that CDC had isolates from both Hawaii and Canada during the last six months.

We mentioned that there was a large cohort of children who have not been exposed to B/Victoria/02/87 HA lineage strains. Basically that would everyone in the United States under the age of 12 years.

Currently the vaccines contain an influenza B virus that's from the other hemagglutinin lineage, the B/Yamagata/16/88 HA lineage. Just to recall again, the actual strains that are in the vaccines being used in the United States in that B/Yamagata lineage include B/Victoria/504/2000 and B/Huangdong/120/2000.

There were studies that were done in adults and elderly. All of these were people who had been old enough to have been very highly likely to have been exposed to the B/Victoria/287 HA lineage strains either through being vaccinated or being infected.

Those studies with current vaccines that included the strains that I just mentioned indicate that those vaccines that induce antibodies that are poorly inhibitory for these B/Victoria/287 HA lineage strains when those have been tested in hemagglutinin inhibition tests. That's not news. That's something that we had been noting for the past 10 years.

I guess I should quickly say that it seems to have become more pronounced in adults and elderly during that period of time. There's just been continuing antigenic drift.

There were some studies with investigation vaccines given to immunologically prime adults that suggested that vaccines with B/Victoria/287 HA lineage components could produce antibodies that would cross-react with the B/Yamagata/16/88 HA lineage strains. To reemphasize, it's in immunologically prime people and not in the immunologically naive.

We don't think that we know how to predict whether the two HA lineages will continue to co-circulate widely. However, in the past what we've seen is that when a newer strain for which there's not very much population immunity starts to spread, that it continues to spread and it certainly can displace the older strains, although there may be some co-

circulation for a while.

Going on, subsequent to our committee meeting, the World Health Organization held it's meeting in February of this year to recommend vaccine composition for the northern hemisphere.

During the WHO meeting there was quite a bit of additional information on surveillance and vaccine studies that became available to us even though that was only a week after our own meeting.

A summary of the information and recommendations, I thin, has been distributed for committee review prior to this conference call. Actually, this information is in the form of a publication and now in the weekly Epidemiologic Record that WHO publishes.

We'll view some of that information on the conference call and there's additional information that has become available since WHO which you'll be hearing shortly. Based on the information that WHO had, its recommendations were for a trivalent vaccine that would contain the antigens of an A/New Caledonia/20/99-like(H1N1) virus, an A/Moscow/1099(3N2) and that would most commonly thought to be the A/Panama/2007/99 stain which is Moscow/1099-like.

WHO recommended a change in the B strain as a B/Hong Kong/330/2001-like strain. Just to remind you, B/Hong Kong/330/2001 is a B/Victoria/287 HA lineage strain. It's not the one that is currently in vaccines. It's the other HA lineage.

There was a question that was raised in the public meeting held by WHO just after its recommendations were drafted. It was stated at that meeting that the B/Shangdong/797 virus can be considered to be a B/Hong Kong/330/2001-like strain.

Just a little bit more information. I'll just also remind you that at our advisory committee, at the Vaccines and Related Biological Products Advisory Committee meeting in January there was quite a bit of discussion about quadravalent influenza vaccine for use in the coming season. I would like to point out some issues that will need to be remembered with regard to how that might happen with influenza virus vaccines.

First of all, although there is some information, there is really not very much relevant information that exist on the safety, immunogenicity and efficacy of quadravalent influence of vaccines produced by current methods.

The current license to activate influenza

vaccines contain 15 micrograms per dose of each hemagglutinin incorporated. The expectation is, as has already been mentioned, that this dose would continue to be true in the absence of data to suggest otherwise.

Any change to the antigen contact, that is, either a reduction in one of the antigens or an increase in the overall amount. Any change in the antigen content for the formulation would require some clinical studies to evaluate safety and efficacy.

Depending on the type of clinical measurement can be made, however, the size of the study could be quite large to reach adequate statistical power. As an example, a well-designed study to assess the impact on adverse reactions that could occur at a rate of about 1 percent as you might see for febrile responses, something that simple would require several thousand participants for each age group examined.

It's not feasible to design and complete clinical studies to support a change to the trivalent vaccine this year. In that respect, even if smaller studies were considered adequate to support the change.

Furthermore, the quadravalent vaccine

would require manufacturers to implement some process and control changes and then they need to validate those in order to satisfy what are considered good manufacturing practices currently.

And then a quadravalent vaccine if it contains 15 micrograms of each strain would just by itself reduce the number of influenza vaccine doses that could be available for the upcoming season. Actually, it would be approximately 25 percent.

The concern is that kind of reduction in vaccine availability could trigger a true shortage of vaccine or result in delays that are similar to or maybe even worse than what we've seen in the past.

There was mention about a quadravalent vaccine containing 7.5 micrograms of each influenza B strain. Although that might not impact the total number of doses, it might, nevertheless, cause a delay in the availability of vaccine both because of the need for clinical information and because, gain, of changes in manufacturing process and control.

Given the fact that the time really is the limiting factor in producing influenza virus vaccines for new formulations, these are really very significant practical barriers that I would say make it impossible to implement a recommendation for a

quadravalent vaccine during this year.

I think I'll stop there and if you have comments or questions, I'll try to answer them.

DR. DAUM: Okay. Thank you very much, Roland. That was right to the point and very helpful as always.

Why don't we open the floor at this point.

DR. POLAND: Roland, this is Greg Poland. Not to side track from the B issue but is this new strain that's A/Wisconsin strain that's been identified, was there adequate cross coverage with currently what we're recommending for next year with the A strains?

DR. LEVANDOWSKI: Well, you're sort of jumping ahead of us. We were going to get to that.

DR. POLAND: It's an important issue and my suggestion --

DR. COUCH: Why don't we do the influence of B.

DR. POLAND: That's fine. Okay. I'm sorry.

DR. DAUM: We will hear about that, Dr. Poland.

DR. POLAND: Okay.

DR. DAUM: Questions about Dr.

Levandowski's presentation, issues that need clarification.

DR. COUCH: This is Couch. Can I make just one comment? That is that Roland has argued very strongly for not taking one of the main lines that I thought should be considered and that was the 7.5. The 7.5 as the component to the quadravalent I would not propose for the many reasons he said, that it be 15 of each of the B components.

He's made the clear statement that that cannot be done without new clinical information and I think that kills the suggestion right there. I'm not sure that we really have much of a discussion on influenza B.

DR. DAUM: Well, I guess, Dr. Couch, I could encourage you if you wanted to be encouraged to say that this might be a desirable goal for the future and that people might begin to do some of the preliminary studies that might make this a possibility for other seasons. I think we've heard pretty clearly that it's not a possibility for this season.

DR. COUCH: Well, I don't think we could resolve that right now as to whether it should be pursued but the discussion is worth considering by people that pursue studies like the NIAID as to

whether this would be an appropriate use of time.

As Roland has pointed out, if you want to find differences between 15 and 7.5 for almost any of the variables that you would like to have, you're talking about -- except perhaps for safety, you're talking about big time numbers.

DR. DAUM: Thank you, Dr. Couch.

DR. COUCH: I don't think we should just shelve the consideration forevermore but I would discourage that subject on this committee.

DR. DAUM: I agree with you.

Other comments about Dr. Levandowski's presentation? Well, then why don't we move on in the absence of them and hear from Dr. Cox if he's ready to go.

DR. COX: Yes, I am.

DR. DAUM: Okay.

DR. COX: I'll try not to shuffle too many papers but I will be moving back and forth from package to package and will try not to make too much noise. Let me know if you hear some interference.

DR. DAUM: Were you just shuffling just for curiosity?

DR. COX: No.

DR. DAUM: There was a lot of shuffling

noise a moment ago. Go ahead.

DR. COX: We'll be careful. I actually have Dr. Fukuda and Primhoff in my office with me --

DR. DAUM: Good morning.

DR. COX: -- to add any additional points.

Okay. We have actually quite a bit of additional surveillance information. I'm actually going to go over some of the H1 and H3 information just to tie up any lose ends or any question marks that might be remaining in people's minds from our previous meeting.

We have summarized the U.S. surveillance information on pages 4 through 7 of the large CDC package that was sent out earlier. We have had one additional report for the week ending February 23. It's fairly clear that influenza activity in the U.S. has continued to be moderate but at last report is still --

DR. DAUM: It cut off, I think. Is still what, Nancy?

DR. COX: Is still increasing. Still moving upward. Also, respiratory specimens that were tested by the reporting labs for the latest week, about 26 percent were positive for influenza. That indicates that there are moderately high levels of

influenza activity continuing in the U.S.

Nearly 7,500 isolates have been identified in the U.S. About 99 percent are Flu A and 1 percent are Flu B. Of the influenza A viruses that have been subtyped, 99 percent are H3 and 1 percent are H1.

Morbidity surveillance indicates that flu activity may still be on the increase and we have two morbidity indices indicating that. The mortality surveillance in 122 city systems indicates that excess influenza and pneumonia mortality has not occurred yet this year.

If we could now turn to page 9 of the large CDC handout. As we stress to the committee, this is nothing new for H1 viruses. I'll be directing H1 and H2 strains that were identified the subject of which was brought up by Dr. Cohen very shortly.

In the HI table on page 9 of the large CDC handout you can see that we have viruses in the reference battery representing vaccine strain A/New Caledonia/20/99 and the previous strain A/Johannesburg/82/96. All of the strains that we've analyzed recently are in the A/New Caledonia group. The vast majority remain well inhibited by antiserum to the New Caledonia virus.

In this particular test we had some

viruses from North America, South America, the Middle East, Asia, and, in particular, we have some strains that we received from China down at the bottom. The story has been very consistent that the H1 viruses that we've received have been well inhibited by antiserum to New Caledonia.

That information is summarized on page 10 in the frequency table. We're looking at the summary of the H1 data generated at CDC. For the last period on October 2000 to current times we've analyzed a total of 50 viruses all of which are related to New Caledonia. A small proportion have actually reduced New Caledonia.

Now I would like to switch subjects slightly and talk about influenza A(H1N2) viruses that have been identified and have receive come press coverage. Between September 2001 and the current time reassortant influenza A(H1N2) viruses have been isolated from outbreaks or sporadic cases in Canada, Egypt, France, India, Israel, Latvia, Malaysia, Oman, Singapore, the U.K. and the U.S.

Studies on representative H1N2 viruses have shown that the hemagglutinin ends of these viruses are both antigenically and genetically similar to that of the New Caledonia vaccine strain. The

neuraminidases of these viruses are antigenically and genetically similar to that of the Panama vaccine strain. Therefore, the current influenza vaccine is expected to provide good protection to reassortant H1N2 viruses.

Now, I would just like to mention that the other six gene segments of characterized H1N2 strains are similar to those of recent A(H3N2) viruses including the Panama and Moscow reference in vaccine strains.

I would also like to emphasize that existing already distributed serological and molecular re-agents can be used for identification and characterization of these influenza A(H1N2) strains.

I don't know if you would like to have anymore information. We've actually in the smaller package on the page that's marked No. 3, the more recently distributed CDC package, we do have a map showing the countries. Actually, Sasha said it's page 1, showing the countries that have H1N2 viruses identified.

I would like to entertain any questions that people might have on H1N1 or H1N2 viruses.

DR. KATZ: Nancy, this is Sam Katz. When was the last time there was any such reassortant where

H1N1 picked up a neuraminidase that was N2?

DR. COX: The last time the reassortant was documented was in 1989 and there were a small number of -- a relatively small number of viruses isolated in China and one identified in Japan that were H1N2. We did some surveillance around that time. The viruses did not appear to spread and were not detected.

You might remember that in the late '70s and early '80s there were H1N1 viruses circulating that had internal genes from H3N2 circulating strength. We assume from everything that we know that the H1 hemagglutinin can quite easily pick up genes from H3N2 strains when there's a mixed infection of an individual.

DR. PALESE: Nancy, Peter Palese. More than 20 years ago we demonstrated that when first H1N1 viruses and H3N2 viruses came along, the internal genes were reassorted. I think it is probably a dead end when these things occur. They have occurred over the last 20 years, these reassortments, between these major H1N1 and H3N2 viruses.

I don't think one should be too much concerned about it. Clearly hemagglutinin is a major antigenic determinant and, therefore, the vaccine will

protect against H1N2 viruses as well as H1N2. Thank you very much.

DR. DAUM: Other comments for Dr. Cox at this point?

DR. COUCH: This is Couch. Peter, you would suggest, would you not, that H1N2 viruses that have emerged could be the clones that remain in circulation or did you suggest that the clone would die?

DR. PALESE: No one can look into the future but in the past these reassortants have not been a major -- they have died out and there is very good reason to believe that those will die out again.

DR. COUCH: Okay. Thank you.

DR. PALESE: But it wouldn't matter really.

DR. COUCH: I agree it doesn't matter.

DR. PALESE: My prediction is, and I don't want to --

DR. COUCH: It might hang around would have been my hunch.

DR. PALESE: I mean, 1978, which is almost 20 whatever years back, we have demonstrated reassortants going on and they have not been the major line since that time. You can never predict for sure

but I think but I think there is very good past evidence that these reassortants are not making it.

DR. DIAZ: Hi. This is Pam Diaz in Chicago. Are you able to hear me?

DR. SACHS: Yes.

DR. DIAZ: I have a question based on those comments and the past history with finding these reassortants in China and Japan only. Looking at the map that we're currently faced with in terms of where reassortants have been identified, can anybody comment on the multiplicity of countries that are involved in those particular countries?

Is it our surveillance system is so good in those areas? Is the spread based on travel patterns? Are these de novo reassortants in these different countries? Does anybody have any thought or information on that?

DR. COX: I do have some additional information. It looks like from the -- we are just developing a lot of information. We are working with our colleagues in the other WHO collaborating centers and national influenza centers to develop a full picture of things.

We will actually go on to page 11 of the big handout because there seems to be quite a bit of

interest in these strains. You will see there is the dendogram for the influenza H1HA gene. All of the viruses of the H1N2 strains that we have looked at so far have HA that cluster together in that top clade. You will see strains from India, Egypt, Texas, and so on in that top clade.

They have their signature immunoacid changes among them. There are some differences depending on the time frame during which they were detected. What we -- and we have some additional information that would allow us to say that there have been at least two separate events.

We don't have complete enough information to know based on travel patterns exactly what's happening. My suspicion is that these viruses have been circulating for a while.

DR. DIAZ: Right.

DR. COX: The earliest strain that's been detected by any of the four WHO collaborating labs goes back almost two years to about April of 2000. These strains have been circulating. We didn't pick them up because we don't do tremendous amount of surveillance for neuraminidase genes. As was pointed out, they are not relevant with regard to changing vaccine strains.

The neuraminidase gene sequence data is summarized in the dendogram on page 13. You can see there that there's a tendency for the neuraminidases of these H1N2 strains to cluster together and they are sort of a third of the way down on the dendogram. We have Nevada/2001, India/2001, and Texas/2001.

I should probably have mentioned that Wisconsin, Texas, and Nevada are the three states in the U.S. from which we have identified H1N2 strains. I think that it is really impossible to predict what will happen. We have seen in the past some lineages of viruses which do not go anywhere. They just die out.

Others that do, and I think at this point in time it's really impossible to predict but as far as vaccine strain selection is concerned have these strains covered so there's no particular worry for our committee.

DR. DAUM: Nancy, do you want to go on and talk about H1N2 and then B or are there more questions about --

DR. KATZ: I've got one more question. Sam Katz for Peter Palese. You're looking at two genes, the hemagglutinin and the neuraminidase. Is there any indication that other of the genes have also

reassorted or is there any suggestion ever that these are hardier strains or more virulent?

DR. PALESE: In the past we have seen some reassortment among the internal genes coming from the H1N1 and the H3N2 line. That has occurred in the past. Is that your question, Sam?

DR. KATZ: Yes. And the question was does that confer any difference in the virulence of the virus?

DR. PALESE: I don't think measurable, if I'm correct. Certainly in mice we have put one or two into mice and haven't seen anything. I mean, I think the answer is I think we don't know and because they have died out, I don't think they are really a major hit. Not very robust.

DR. DAUM: Thank you very much.

DR. COX: I think that some of the early H1N2 reassortants were actually put into people back in the late '70s by Paul Bear, The Common Colds research lab. There were not differences, detectable differences in virulents.

In addition, when they were circulating widely during the late '70s and '80s there was no indication they were causing more serious disease than other H1s. We've had no indication so far that

they're causing more serious disease than H1, although we do have limited data.

Current strains, as I mentioned before, I just want to clarify, do have only the H1 gene from currently circulating H1N1 viruses. All other genes are H3N2.

DR. DAUM: Thank you very much. Other questions regarding H1N2 or H1N1? Let's go on then. Nancy, would you like to continue?

DR. COX: Sure. On page 15 of the large CDC handout, you'll see an H3 test. It was performed on the day after our meeting, our last meeting. On that test we have a number of strains from the U.S. as test antigens followed by a number of stains from China and the last three strains from Singapore.

Among the H3 viruses tested recently, only a handful show a reduction of four fold or greater compared to the homologous side of the event in strain. You'll see that the antigen No. 24, which is called CNIC/114 is a virus that was isolated from a patient in Beijing during the January outbreak there. You'll see that there's a titre of 160 against the Panama antigen as compared to a titre of 640.

We had sequence information that indicated that the Chinese viruses might be somewhat different

from viruses circulating in other parts of the world so we took that CNIC strain, put it into ferret, and you'll see the result on the table on page 16.

On page 16 we have a lot of very recent strains isolated in the U.S. tested in a cross test with the CNIC/114/Beijing strain. You will see that the strains depicted on this table are very well inhibited by antiserum to the Panama vaccine strain.

Furthermore, we can't really see any advantage if we look at column F where we have antiserum to the CNIC strain we can't see any significant advantage in this antiserum. We don't really have a new variance among the Chinese strain. I think that is just by way of reassuring the committee that we look very thoroughly at a lot of additional information.

If you would please turn then to page 17. We have a summary of the HI information that's been generated at CDC. If you would just look at the October to February -- October to the present time period you can see that we've tested a total of 255 strains here at the CDC as compared with 125 at the time of our January VRBPAC meeting so we have really generated a lot of additional information.

We have only a very small proportion of

stains which are reduced and titred to the Panama strain. As you can see here, we only have seven out of the 255, that is 3 percent.

Okay. Now, the most up-to-date HA sequence data is on page 18 of the handout. I won't really go over this in detail. I just wanted to point out about two-thirds of the way down you can see a small grouping of viruses from China including the CNIC/114 strain which was shown in the HI table. You can see that all of those strains starting with the Hong Kong/1269 strain up to the CNIC/114/2001 strain have three signature amino acid changes.

In summary, I would just like to reassure you that we haven't found any new variants, even though we've looked at a lot more viruses and we feel we've looked very carefully at the viruses that were causing outbreaks in Northern China during December and January during this season.

Are there any questions about the H3N2 strains? If not, I'll move onto the B strains which are really the challenge for today. If you would turn to page 20 of the large handout. I'm sorry for shuffling paper here but if you would also look at page 2 from the shorter handout that was sent.

In these two A type tables we have viruses

from a number of different locations and quite a number of strains from the U.S. in particular. We have at the top as reference antigens two blocks of antigens. The first starting with Sichuan/379 we have strains that represent the current vaccine strain all of which are related to each other. Then on the right we have the Beijing/243 Hong Kong/22 and Hong Kong/330 strains which are all on the Victoria lineage.

It's very easy to distinguish these two groups of viruses using culture section ferret serum, as you can see on both tables. There's relatively little cross reactivity between viruses that are on these two separate lineages.

You can see also -- I think this is an important point -- that there are a number of strains that have been isolated relatively recently that are in the Sichuan/379 grouping of viruses that have reduced titres to the Sichuan/379 antiserums as well as to the B/Vic/504 antiserum. We have seen this at our lat meeting and we've seen increasing numbers with reduced titres and I just wanted to point that out.

Now, among the B/Vic lineage viruses, that is, those that are on the right side of the tables on pages 20 and 2, we see that the strains are most closely related to the B/Hong Kong/330 strain which is

an egg isolate which has been sent out to vaccine manufacturers for evaluation.

I think I will move now to page 3 of the short handout. I would like to summarize briefly the circulation of B/Victoria lineage viruses. You can see that there are a number of additional countries that have been included since our last meeting. I don't know if you need me to list the countries but there are additional countries in Europe, in the Middle East. Of course, we have added the United States to the map since we last met.

The countries in Europe are the Netherlands, Italy, Switzerland, and there's Israel and Oman in the Middle East. I think that fairly well covers it. The viruses have freely taken off and are spreading.

Now, I would like to go to page 4 but I have to apologize for some typos that exist. You will just have to listen to what I say rather than what's in front of me. We had a mistake where we had the 11 viruses that were listed as being B/Hong Kong-like were actually not from Central and South America.

We have of the 90 influenza B viruses that we have done HI testing for that were isolated between October 2001 and the current time, 43 percent of them

are B/Hong Kong/330 or B/Hong Kong/22-like.

About 32 percent are Sichuan-like vaccine-like and about 25 percent have reduced titres. They are Sichuan group viruses but they have a reduced titre against the Sichuan antiserum.

We've actually been able to use molecular analysis to look at additional strains that we have shown on page 5 of the short handout. If you look at the bottom time period you'll see that of 134 strains that we've analyzed using molecular technique 41 percent are Vic-like and the remaining 59 percent are related genetically to the current vaccine strain.

On page 6 of the short handout you will see some additional information that we've obtained either from national influenza centers directly or from our sister collaborating center in London. Also our collaborating center in Tokyo, Japan.

We were trying to get more complete information than what we have for the viruses that are actually sent in to us for analysis. If we look for the U.S. of the 22 strains that we've analyzed for our B/Hong Kong/330-like and 18 are related genetically to Sichuan.

Canada we have an update today. They have a total of 68 influenza B strains and 64 are B/Hong

Kong-like B/Victoria lineage viruses. In the Netherlands three out of 23 are Victoria lineage. Italy 13 out of 74. In Hong Kong the vast majority of strains 113 or 93 percent of recent B strains are Vic lineage strains. In Japan also there is a majority. About 82 percent of the B strain is B/Vic lineage viruses.

I think that fairly well summarizes the B information so I'll entertain any questions that you might have at this time.

DR. DAUM: The floor is open. Thank you very much, Nancy.

Questions for Dr. Cox?

DR. PALESE: Peter Palese. Nancy, have you tried to do a neutralization test? In other words, the ferret sera are notoriously very discriminating and may give us a fuller picture in terms of hemagglutination in a patient.

Most importantly rather there is a neutralizing activity. Do you have, for example, mouse antisera of the Sichuan-type and how good would it neutralize the Hong Kong vintage and vice versa. I am really concerned that the hemagglutinin and inhibition may accentuate differences which may not be as important.

DR. COX: Yes, Peter. We haven't done any studies -- any neutralization studies recently but we have done them in the past. The Victoria strain viruses are really quite distinct both by HI and by neutralization using a variety of different antisera.

DR. PALESE: From different species.

DR. COX: Yes. We've used sheep serum and human serum and ferret serum.

DR. DOWDLE: Nancy, this is Walter Dowdle. I wonder if you could give us some idea of the information that has accumulated since the WHO meeting in February? In other words, what have been the trends since that meeting in view of the data that you've now summarized here?

DR. COX: There have been increasing isolation of B/Vic-like strains, increasing identification and isolation of B/Vic-like strains. We had no U.S. strains at the time. We had no strains reported from Switzerland or Israel. We did have Italian strains and one strain from the Netherlands reported at that time. In addition, in Japan there were at that time about 50 percent of B strains for B/Vic-like. Now over 80 percent are B/Vic-like.

DR. DOWDLE: Thank you.

DR. COX: There have been quite a lot of

additional strains identified in Hong Kong.

DR. DAUM: This is Bob Daum speaking. Just crudely grouping the countries on page 6 by sort of continent, Japan and Hong Kong seem to be of similar trends and Italy and the Netherlands seem to have similar trends. The U.S. and Canada seem to be almost diametrically opposed to each other. I wonder if you could comment whether that's a centennial site for the sample thing or why are they so different, if you have any idea?

DR. COX: We don't really know. In fact, we were discussing that very issue this morning. It could reflect a later introduction of these strains into the U.S. and Canada. We know that there was, for example, a well documented travel-related case. About a year ago someone returning from China to Canada who had been visiting there actually was diagnosed with B/Vic-like strain.

And we're actually -- Sasha is just telling me that today we have four more B/Vic-like strains that we identified from the U.S. That makes it eight out of 26.

DR. DAUM: Other comments or questions?

DR. KOHL: Yes. This is Dr. Kohl. Nancy, obviously the question is where are we going. Can you

give us some kind of a temporal sense whether we're seeing a real fall-off in the Sichuan-like viruses and a major upswing or whether they are both going on at the same time?

DR. COX: The situation is pretty complex, Steven. It's pretty hard to say where we're going. We may be going different places in different countries which makes it even more difficult. Clearly there is an upswing in B/Vic-like lineage identification. That's very, very clear. Whether there's a decrease in Sichuan it's hard to say.

When we had the opposite situation occur in 1989, '90 when the Yamagata lineage strain spread from Asia to the rest of the world, we had co-situations in some countries for a year or two. But in other countries the Yamagata lineage viruses just really took off and supplanted the Vic lineage viruses within a very short period of time. I think it is very difficult to predict.

DR. DIAZ: Nancy, this is Pam Diaz again. Just a quick clarification. Looking at that chart that you had sent on the characterization of Flu Bs, the one that you just went over, the U.S., Canada, etc.

DR. DAUM: Page 6 or page 20, Pam?

DR. DIAZ: What time frame is that over?

DR. COX: October to the current time.

DR. DIAZ: That's what I thought. Just in commenting many between the U.S. and Canada in that dichotomy, if you stratify all those strains from both of those countries over time, does that give you any better clue as to what's going on more recently. Also, do you think the small numbers in the U.S. compared to Canada may have something to do with dichotomy also?

DR. COX: Yes, I do. We are really beating the bushes to get as many strains, as many viruses sent to us from U.S. labs as possible. We have been for some time. It takes quite a few weeks to actually get the viruses here.

We have another 60 or so viruses that have been isolated in the United States that we haven't had our hands on yet. I suspect that once we actually get the collection of those viruses and if we look at the viruses.

If we look at the viruses at the northern tier of states, we see that we have more and more B/Vic-like strains -- a greater proportion of B/Vic-like strains, particularly in those states. But we don't have our hands on the viruses yet. Now, in

terms of statamine by time, we just have too few to really, I think, pick up trends.

DR. DIAZ: Okay.

DR. COX: But in Canada, clearly B/Vic-like strains are predominating and they did not last year.

DR. LEVANDOWSKI: This is Roland Levandowski. Can I make a comment?

DR. DAUM: Of course.

DR. LEVANDOWSKI: If you consider North America as one place and looked at the numbers there, I guess it's around 75 percent of the strains that would be B/Victoria/287-like.

One other thing that's happened in terms of epidemiology even in the United States is that sometimes at one end of the country we see a predominance of one type of virus and at the other end another type.

I can think of a recent example about five years ago where the H3N2 viruses, I think, were predominant on the West Coast at the same time H1N1 viruses were predominant on the East Coast so there can be some of that kind of dichotomy.

I guess I'm sort of maybe viewing North America in a similar fashion with the northern part of

North America and then the southern part of North America. There may be a little bit dichotomy there on which of these lineages seems to be the predominant one.

DR. DAUM: Okay. Other comments or questions of Dr. Cox?

DR. EICKHOFF:Question from Ted Eickhoff for either Nancy or Roland. How many years now have viruses from the Yamagata lineage been in the vaccine? It's been at least, hasn't it?

DR. LEVANDOWSKI: This is Roland. It's been since 1988 that we've had B/Yamagata/1688 lineage strain in the vaccine in the United States.

DR. EICKHOFF: So my guess was a little bit off.

DR. LEVANDOWSKI: Before that for about -- I take that back. For about two or three years I think there was a B/Victoria virus in the vaccine.

DR. EICKHOFF: Okay. Thank you.

DR. DAUM: Other questions or comments for Dr. Cox?

DR. STEPHENS: Nancy, this is David Stephens. The recent four isolates that you just updated us on, what can you tell us about their location?

DR. COX: New York. Additional ones are from New York.

DR. STEPHENS: Okay.

DR. DAUM: Other input?

DR. PALESE: Peter Palese once more. Nancy, can I get a quantitative feeling for how much the neutralization is different if you're using Yamagata against Victoria and the Victoria antiserum against Yamagata?

DR. COX: I think that the most helpful, the most useful information is actually from human serology rather than from the animal. I think that Ron will be commenting about those in his next presentation.

DR. PALESE: Okay.

DR. DAUM: Are there additional comments for Dr. Cox? If not, I would like to move on to Dr. Levandowski for his second presentation.

DR. LEVANDOWSKI: Okay. I'll just jump in and go right ahead. Maybe I'll try to answer that last question a little bit before mentioning anything else.

What we have been seeing routinely over the last 10 years when we've looked at human serology with vaccines containing B/Yamagata lineage

hemagglutinin that the cross-reactive antibody responses for the B/Victoria lineage strains. Although it was reasonably good in the early years after the Yamagata strains were added to the vaccine, at least in immunologically primed adults, it's never been good in immunologically naive people like children.

Even more impressive, I think, is over the last four or five years we've seen the antibody responses of immunologically primed adults going down as well so that often for some of the serologies we look at there may only be in terms of the geometric mean titres there may be somewhere between a 70 and 90 percent reduction comparing the geometric mean titres against the non-vaccine B/Victoria lineage to the vaccine B/Yamagata lineage in hemagglutination inhibition.

DR. PALESE: Migration is neutralization which is a much more relevant parameter than hemagglutination inhibition.

DR. LEVANDOWSKI: Um, I don't think I can answer you on neutralization. There were some studies that were done using single radio hemolysis.

DR. PALESE: My point is maybe it's not that bad as we have the data here that there is some

cross-neutralization which is very important.

DR. COX: Peter, with animal sera there was limited cross-neutralization. The neutralization data reflected the HI data quite well. I would have to go back. I can't give you a quantitative estimate but I do think the HI results with human post-infection human sera are really what we rely on for vaccine strain selection whether it's B or H1 or H3. I think those data are very relevant.

DR. LEVANDOWSKI: Maybe I could add a little bit to that. There was one study that we did in young children which included a comparison of hemagglutination and neutralization titres. In that instance children who had been recently -- there were some children who had been exposed to B/Victoria-like strains and when they were exposed to B/Victoria-like strains and were immunized with the Yamagata vaccine, they developed neutralizing antibodies to both.

But if they were immunologically naive, again they did not develop hemagglutination inhibition or neutralizing antibody titres. That doesn't answer your question entirely but there was a pretty good correlation between the hemagglutination inhibition titres and the neutralization titres, at least in that study with children.

Perhaps I should go on in the interest of time. First I'll tell you about vaccine studies and then some information on the strains and re-agents. There was additional information that was made available to the WHO in February in it's deliberations.

What I can say is that generally that information was raised similarly to what was already presented in our meeting in January. I say that the information supported both the WHO recommendations and the recommendations that had previously been made by our committee.

With respect to the serological information I only have a very few comments that I think are relevant to the discussions. One, there were studies -- studies have been done that have included -- serologic studies that have included those H1N2 strains and at least two of the strains that were included in the serologies that were H1N2 were the A/Wisconsin/12/2001 and the A/Egypt/96/2002 strains.

Really overall there weren't any differences in the serologic responses for the H1N2 strains as compared to A/New Caledonia/20/99 or any of the other H1N1 strains. Again, that's hemagglutination inhibition assays.

We heard in January from CDC about a clinical study that used B/Beijing/243/97 virus and that, again, is in the B/Victoria 287 HA lineage. That strain was contemporary with the B/Shangdong/797 strain that you might remember was used for commercial production for vaccines in Asia during 1999 and 2000.

The results that CDC presented in January indicated that B/Beijing/243/97 containing vaccine produced antibodies in adults that cross-reacted very well with the B/Harbin/794 strain which is a B/Yamagata lineage strain.

In addition, there were some clinical studies that were done using an investigational vaccine that was made available to NIBSC in the United Kingdom. They've made some of those results available to us for the discussion today. I've been given permission to provide a summary of the data for the committee.

The vaccine that NIBSC used for the study was a trivalent vaccine that had 15 micrograms per dose of each of the following antigens. It had an A/Sydney/597(H3N2) component, an A/Beijing/26/296(H1N1) component, and a B/Shangdong/797 component.

That vaccine was given to 30 adults and 30 elderly and it has to be presumed that all of these

people were immunologically primed and probably had been exposed in their lifetimes to both B/Victoria/287 lineage strain and also B/Yamagata/16/88 lineage viruses.

The sera that were tested were pre-immunization and three weeks post. In addition to the B/Shangdong/797 vaccine antigen, several additional viruses including a number of B/Victoria/287 HA lineage strains were tested.

In looking at the cross-reaction between the B/Shangdong/797 virus and the B/Yamagata/16/88 HA lineage viruses, there were reductions seen there. They were not severe but some of them were as much as 50 percent. Overall I would say that it was encouraging that there was a reasonably good antibody response to those non-same HA lineage strains.

The B/Victoria/287 HA lineage strains that they've tested also included a number of the recent strains that we've been talking about today including the B/Hong Kong/330/2001 and the B/Hawaii/10/2001. They had some other strains from Italy and also from Hong Kong.

In terms of the post-immunization geometric mean titres, all of these more recent B/Victoria lineage strains that were tested had titres

that were equivalent or higher than what they found for the B/Shangdong/797 strain with one exception.

There was one of the Italian viruses, B/Genoa/124/2001, that gave geometric mean titres that were about 35 percent lower in adult population and about 51 percent lower in the elderly. Really to repeat, all of the other B/Victoria/287 HA lineage strains were inhibited at similar titres to the vaccine strain which is an older one.

I guess what I should say is that overall, I think, what the results indicate is that the B/Beijing/243/97 and the B/Shangdong/797 vaccine strains induced what were really pretty good cross-reacting antibodies for both of the HA lineages in the immunologically primed adults. Maybe I should just stop and see if there are any questions on that part.

DR. DAUM: Any questions for Dr. Levandowski?

DR. COUCH: No children sera in Europe either?

DR. LEVANDOWSKI: We do not have access to pediatric population at this point. That's right.

DR. DAUM: Other questions? Roland, why don't you go on.

DR. LEVANDOWSKI: Okay. So we also have

some information about how things would perform in manufacturing and also on the availability of re-agents. I had previously -- we had previously mentioned here from the Center for Biologics that for the H1N1 and the H3N2 strains manufacturers already have seed viruses that are good for production and there are re-agents for potency testing available.

I should point out that there's been a really -- for those of you that are on the line, you might want to know there's been a really unusually large demand for re-agents both for manufacturers and from other national authorities. I think it relates to the success of use of influence of vaccines.

As a result, I think we are going to need to produce and calibrate new batches of standard antigen for both the H1N1 and H3N2 strains for this year. We expect that the timing for availability of those re-agents will have no impact on production schedules, but it does mean that we're be continuously assessing our inventory and we may need to adjust the amount shipped to people who request it just to be sure that we can supply everyone in a timely fashion.

As far as the B strains go, we already had the re-agents, as mentioned, for the B/Victoria/504/2000 and B/Guangdong/120/2000 vaccine

strains. We also have a supply of potency re-agents available for the B/Shangdong/797 strain since that one had already been used for manufacturing earlier, as I mentioned.

If there are any other strains that are chosen, of course, we'll have to make potency reagents for that. We would anticipate that as usual we would at the earliest have those new re-agents available in May.

There are several influenza B strains that are being assessed as candidates for suitability for manufacturing and the ones that the manufacturers have spent the most time looking at at this point are B/Hong Kong/330/2001, B/Hawaii/10/2001, and B/Shangdong/797.

What we've heard so far is that probably further work is necessary with all three of these strains, but it seems that as time as gone on since our meeting in January that there's been some improvement in yield. What I've been hearing is that what the yield seems to be somewhere in the range of 75 percent to the same as the current influenza B vaccines, which is actually relatively good news. Again, the work isn't really complete and it may even be possible to identify some additional strains that

could be assessed to see if there's any advantage.

Again, I think the good news is that some of these strains that are being evaluated seem to hold some promise including the B/Hong Kong/330/2001 strain itself that was selected or recommended by WHO. Again, I think that is really all I need to say here unless there are some questions or comments.

DR. COUCH: This is Couch, Roland. Was there any discussion of a quadravalent vaccine at the WHO meeting in Geneva?

DR. LEVANDOWSKI: Yes, there was. The concerns expressed at WHO were similar to what I had mentioned at the outset. There's a concern that it may be difficult for regulatory authorities around the world to be able to assess the vaccines and how they are being produced. That was discussed. It was a conscience decision.

DR. DAUM: Other questions for Dr. Levandowski? Then I guess we can proceed. Roland, can we ask you at this point to do your options analysis?

DR. LEVANDOWSKI: Yes. Nancy Cox was going to do that.

DR. DAUM: Oh, sorry. Great.

Dr. Cox.

DR. COX: Yes, I'll do that. I would first like to mention that we've been very busy trying to isolate some additional B/Vic-like strains in eggs and we were quite successful actually and have four more B/Vic lineage strains to send out to the manufacturers this afternoon.

I just wanted to let people know that those re available. We had been proceeding without knowing that the B/Hong Kong/330 and Hawaii viruses are growing better now for the manufacturers.

Okay. So now I'll go on to recap the information for the influenza B viruses and then summarize the option.

First of all, there are two antigenically and genetically distinct lineages of B viruses represented by the Sichuan/379 strain, the Hong Kong/330 strain. Antigenic drift has been detected in both lineages. There is evidence that some influenza B viruses in the vaccine HA lineage are less well inhibited by antisera from people immunized with current vaccines.

Strains in the B/Vic HA lineage have been isolated in a number of countries and continents where they have not previously been found. Stains in the Vic HA lineage are poorly inhibited by antisera from

people immunized with the current vaccines containing B/Sichuan/379-like viruses.

Vaccine studies indicate that one HA lineage may produce antibody responses to the other lineage in immunologically prime persons. But previous studies that have been done indicated that was not true in unprimed individuals.

The Sichauan-like strains that have been mentioned, Johannesburg/5, Victoria/504, and Guangdong/120 are being used for manufacturing current vaccines. The Beijing/243/97 and Guangdong/797 stains have been used in production of experimental vaccines used for commercial vaccine that had been marketed in some parts of Asia.

As we know from our meeting in January, influenza B viruses from both HA lineages have been sent to the manufacturers for evaluation for a vaccine production. The options really are, (1) to retain the current B Sichuan-like vaccine strains. The pro would be that manufacturing is well-defined and relatively predictable.

Against that position is the fact that new variant strains have been identified in the vaccine HA lineage, and strains in the Vic HA lineage are appearing in increasing numbers and in new regions of

the world.

Some influenza B strains, particularly those in the Vic HA lineage are not well inhibited by post-infection or post-immunization antisera.

Option No. 2 is to update the vaccine strains to a more recent B/Sichuan lineage virus. Now, the pro to this approach would be that vaccines mist provide better coverage for current influenza B viruses in that lineage.

Several Canada strains were identified and they were being examined for suitability by manufacturers although certainly less attention has been given to these strains.

Against option 2 is the concern that a new strain may not provide superior immunogenicity and efficacy compared to the current vaccine, and the fact that new influenza B strains may cause difficulty to manufacturers which is true for any update that we might do.

And that a new B/Sichaun group virus would not be expected to provide better cross-protective antibody against B/Vic lineage viruses than the current vaccine.

Option 3 is to change the current vaccine strain to a representative virus on the B/Vic lineage

such as B/Hong Kong/330 and similar viruses. The pro to this approach is that B/Victoria lineage strains have spread beyond Asia to North America to Europe and predominate in some countries.

B/Vic strains have been identified in the continental U.S. for the first time in over 10 years so there is a fairly large cohort of children; that is, virtually everyone under 12 years of age that are unprimed for this virus.

Most adults, though they are immunologically primed, have fairly low antibody levels to current B/Vic lineage viruses. We have seen this to some extent in the serologies that have been done here, but it was very apparent in data that was presented at the WHO meeting from Japan where they've done a sera survey in a cross-section of the population.

Even though B/Vic-like strains have circulated at low levels, there is very little antibody to these strains compared to the levels of antibody to the current vaccine strains.

We know that current vaccines containing the B/Sichuan-like strains do not induce antibodies against the current Vic lineage viruses or high levels of antibody. Investigational vaccine containing

Shangdong antibodies again type B, the trial lineage strains including Hawaii/10, B/Hong Kong/330, and others that Roland mentioned.

And in immunologically prime persons investigational vaccines containing Shangdong/797 virus induces antibody levels to the Yamagata lineage strains, although in some cases at a bit reduced level compared to the B/Vic lineage strains.

Against moving toward a B/Victoria strain is that B/Yamagata or B/Sichuan/379 lineage viruses may still circulate and may process and become dominate again. We don't know for sure that they are going to die out.

We know from previous studies in immunologically unprimed children that production of antibodies against the nonvaccine influence of B/HA lineage would not be expected. There is some danger in moving to a B/Vic lineage virus. In any case, whenever we change vaccine strains, as I mentioned before, we have the uncertainty about how those particular strains are going to perform with regard to production.

I'll close there. I think we're ready for any questions or discussion.

DR. DAUM: Let's open the floor to just

that. We've heard the options and perhaps there is additional clarification you need or points you want to raise.

DR. COUCH: Couch. If you were selecting a variant of Sichuan, what would the selection be? Do you have a candidate? I don't think that's where we're going but I would be interested in that as an option.

DR. COX: We had sent out some additional strains and perhaps will have some information about how well they grow later on. We had sent out a Sichuan/379. There are some strains available.

DR. COUCH: The data in the cross-reference charts, I didn't see any convincing drift of viruses. That was the reason for the question. That's all right.

DR. COX: It's the Shizuoka/15 and the Sichuan/317 strains, and I think we sent one or two more strains out to the manufacturer.

DR. DAUM: Other comments or questions?

DR. DECKER: Michael Decker. A question and then probably a comment. The question is do we have manufacturing representatives from any of the manufacturers online to offer any update on performance of the candidate B/Vic lineage strains?

Hearing none, then I'll offer a comment.

It's my understanding that we are having reasonable success with the B/Hong Kong strain that WHO nominated as the preferred recommendation. It's not reaching the levels yet of what we've accomplished with Shangdong but it's reached the level where it's a reasonable choice and from our point of view concerns about the manufacturing capability of that strain does not need to inhibit the choice.

It's my understanding, but I would love to have it confirmed, that Whyafus is reasonable success with the Hawaii strain. I haven't heard how Powderject is doing.

DR. LEE: This is Stan Lee from Adventist Pasteur. I just wanted to confirm what Dr. Decker has said and also what Dr. Levandowski has said. Our experience with the B/Victoria lineage is it has reached about 75 percent of typical yields for B strain production.

DR. DAUM: Okay.

DR. DECKER: The final comment on this is that given the impression I have, the different manufacturers are having differential success with various strains in the B/Vic lineage. I would recommend that if the committee votes to switch to a

B/Vic lineage strain, that it authorize -- that it vote for that lineage but leave the selection of the specific working strain to the manufacturers in collaboration with the FDA and CDC.

DR. DAUM: Other comments or input? Okay. Perhaps we will proceed then.

DR. KOHL: This is Steve Kohl.

DR. DAUM: Hi, Steve. Go ahead.

DR. KOHL: I'm feeling very uncomfortable with the options that are outlined. It does not appear to me that we have a very strong feeling as to which B lineage is going to be circulating in the U.S.

As usual, if that is the case, then the people who are going to be left the most uncovered whatever we do if we are restricted to only one B selection are the young children, the children who have not been primed. I'm very uncomfortable with that.

I wonder if there could be some discussion in the committee. I wonder if Dr. Levandowski could comment about the absolute impossibility of a quadravalent vaccine is really where we are if it's that impossible.

DR. DAUM: Dr. Levandowski, perhaps you should initiate a response to that.

DR. LEVANDOWSKI: I think it would be probably at this point in time impossible to have a quadravalent vaccine and have it available in time for use in the market and meet everybody's needs to have a vaccine available.

I tried to point out that there are a number of issues, not just the numeric ones but some real issues in terms of how manufacturing gets done to accommodate good manufacturing practices, and also questions that I think would be ones that we want to see answered for making what would be a relatively aggressive change in what the vaccines have done.

I guess I would mention one other option. Maybe not an option but an alternative strategy that has been discussed in the past in our meetings. Not recently but in the distant past. The same kind of discussions came up actually when the change was made from the B/Victoria/287 strain to the B/Yamagata/1688 strain in 1988.

That recommendation was made actually without B/Yamagata/1688 strain ever appearing in the United States and was based on the rapid spread of those strains in Japan and maybe a few other countries in Asia.

Although it is unpredictable what happened

on that occasion was that once that strain started to move, in the United States at least it just placed entirely the B/Victoria type strains and in Europe it was about 50/50. Subsequently it was all B/Yamagata-like.

What was discussed at the time was the concern that there might be unprimed children who if the vaccine contained only B/Yamagata/1688 would be susceptible to B/Victoria/287. There was discussion about the possibility of a monovalent supplemental vaccine that could be used.

Some of the issues that were discussed, and I think Dr. Couch and maybe Dr. Eickhoff will remember some of these discussions, but the issues got down to very practical ones about how do identify who should get the vaccine and then the logistics of getting that vaccine to the point of use.

Nevertheless, there was an effort to hold on to what was material that had been used for making the B/Victoria/287 vaccine to keep that stored in the event that it was something that would be thought to be necessary. I guess at this point we are still relatively early in the season.

Nancy Cox mentioned that the numbers are still going up and sometimes as time goes on the

epidemiology really does indicate very clearly where things are going to go. Sometimes there is what we term a herald wave where a late outbreak or late portion of the influenza season turns to a different strain and it seems to be the strain that sometimes becomes the predominant one the following season.

I don't know if we're seeing that with influenza B. It doesn't seem to be because of the number of isolates at this point but that is something that may help to clarify. What I'm trying to say is I think that there is another possible solution for some specific population but not a very good solution because of the logistics but still a potential solution.

DR. EICKHOFF: This is Ted Eickhoff. Again, I do remember those discussions, Roland, from over a decade ago. I think Dr. Kohl is reflecting the discomfort that anybody feels when they are trying to anticipate what is going to happen next year.

Based on what we've learned in our January meeting and today again about how the B/Vic lineage strains are spreading, I would have a high degree of -- I think there is a high degree of likelihood that we'll see that predominate in the United States next year if, indeed we have a B year next year.

DR. LEVANDOWSKI: I agree. I agree.

DR. DAUM: Can we take some comfort, Roland, or Nancy, that only 1 percent of the strains that have been recovered this year have been type B in the first place? Therefore, this uncertainty that Steve is certainly expressing for all of us is a relatively minor contribution to the overall epidemiology or is that not necessarily the case?

DR. COX: I think that what we're trying to do is anticipate what will happen next year. It could actually have a fairly B year next year. Based on our past experience with B viruses and with influenza in general, I would tend to think that we are likely to have a relatively -- we may have B next year and we are likely to have B/Vic-like viruses.

We may have some Sichuan-like viruses circulating as well. It's just impossible to predict. The fact that we had low-levels of activity this year doesn't help us say what's going to happen next year. It actually makes it more likely that we'll have a lot of B next year.

DR. POLAND: And aren't we, Nancy -- this is Greg Poland -- led by the knowledge that there is relatively low levels of, let me use the term, herd immunity out there to the B/Victoria-like viruses?

DR. COX: Yes. Correct.

MS. FISHER: Excuse me. Barbara Fisher.

DR. DAUM: Hello.

MS. FISHER: Hi. I have a question. Is B/Victoria virus, is that B/Victoria flu a more virulent flu than A?

DR. COX: No, it is not.

MS. FISHER: Thank you.

DR. DAUM: Other questions?

DR. KIM: Bob?

DR. DAUM: Yes.

DR. KIM: This is Kwang Sik Kim. Quick question. As we heard, there was a trend toward the increase in B/Victoria lineage but it is unclear how it is going to pan out in the U.S. Certainly data is still coming to the U.S.

The question is that when will perhaps would be the latest time that we have to make a decision on a list of B. With those numbers coming in maybe lower but to give us a little bit more assurance that initially we report four out of 22 and now it's eight out of 26.

Let's say four or six more coming in within the next week or two maybe tied to the Victoria lineage so I think there is some sort of assurance of

keeping involved. My question is when would the latest time that we have to make a decision on this?

DR. DECKER: We're there. Michael Decker here wearing my industry rep hat. I think all three manufacturers I think would be very uncomfortable with the committee failing to select one single B lineage today.

DR. MIDTHUN: This is Karen Midthun. I just want to make a point getting back to what Roland was saying earlier. I just wanted to clarify.

DR. DAUM: Dr. Midthun.

DR. MIDTHUN: Yes. I'm sorry. This is Karen Midthun. I just wanted to clarify that with regard to what Roland was saying earlier that a discussion at an earlier time point back in 1988 had been the potential to use a monovalent B vaccine in addition to the trivalent that was in use. As Roland said, there were a number of considerations and difficulties perhaps with implementing something like that. Thank you.

DR. DAUM: Other comments or input before we start pulling?

DR. SACHS: This is Jody Sachs at the FDA. I wanted to at this time before we open up a vote, I wanted to open it up for a public hearing. I'm going

to ask the people here. Nobody has come forward so far but is there anyone in the room who would like to address the committee at this time?

DR. DAUM: Committee comments first?

DR. SACHS: I don't see any -- there's no one coming forward right now. Thank you.

DR. DAUM: Okay, Jody. Are there other comments from committee members? Okay. Well, I think it's time to solicit an opinion about what to do here. The question for this session is what strain should be recommended --

DR. SACHS: Excuse me one second. Is it possible, Dr. Daum to pick up your handset and just talk from that while you read this? It's still hard to hear you. Thanks.

DR. DAUM: Is that better?

DR. SACHS: Yes.

DR. DAUM: The question is what strain should be recommended for the influenza B component of the 2002/2003 vaccine? The list I have in the absence of a seating arrangement is an alphabetical one. I think I'm going to take chairman's prerogative and ask Dr. Couch to initiate the discussion. Then we will go down the list in alphabetical order.

DR. COUCH: All right. I'll comment. I

don't actually think the discussion is a very complicated one. I'm being redundant, I know, but I was leaning toward what might be called the cautious conservative view of splitting it between the two B candidates but I would not have done 15 of each. I would have done seven and a half of each.

Roland has made it very clear to us from a regulatory point of view that's not really an option and might even be a problem for manufacturers. I think it's very clear that we have to select a single antigen and that certainly could be considered a standard decision anyway.

I think the data is very clear and I think we said that back in the original meeting as well that it has to be Victoria. The only discussions we've had otherwise is to whether we might also need to consider B/Sichuan derivative.

Since that is still at the discussion stage only as a backup should it become necessary. I think our recommendation is very straightforward that we harmonize with the WHO and that we recommend that the B/Hong Kong/330-like strain.

DR. DAUM: Dr. Couch, I might ask you and subsequent committee members as well to weigh in on the suggestion of Dr. Decker, that we allow some

flexibility with the choice that you make.

DR. COUCH: I think we traditionally do that when we say B/Hong Kong/330-like strain.

DR. DAUM: Right.

DR. COUCH: And then the actual strain is always decided between the manufacturers and CBER.

DR. DAUM: So the answer is yes?

DR. COUCH: The answer would be yes, correct.

DR. DAUM: Thank you very much.

Dr. Aguilar-Cordova.

DR. AGUILAR-CORDOVA: Yes. I would agree with what Dr. Couch said.

DR. DAUM: Very good. Any additional comments?

DR. AGUILAR-CORDOVA: No.

DR. DAUM: Okay.

Dr. Diaz. Dr. Diaz, are you there? Dr. Diaz?

Dr. Dowdle.

DR. DOWDLE: Yes. Walter Dowdle. I agree with Dr. Couch.

DR. DIAZ: Dr. Diaz. Can you hear me?

DR. DAUM: Oh, hi. There you are. Yeah, I didn't hear you before but we can hear you fine now.

DR. DIAZ: Good. Thanks. I would just weigh in with the same comments, that I would prefer changing to B/Hong Kong/330-like strain.

DR. DAUM: Thank you very much.

Dr. Eickoff:

DR. EICKOFF: I concur.

DR. DAUM: Dr. Faggett, are you here? I think he might not be. We'll come back.

Ms. Fisher.

MS. FISHER: I concur.

DR. DAUM: Dr. Goldberg.

DR. GOLDBERG: I concur.

DR. DAUM: Dr. Griffin was not here before. Is she here now?

Dr. Katz?

DR. KATZ: This is Sam Katz. I'd like to confer -- concur.

DR. DAUM: You can do both.

DR. KATZ: I would add one caveat. I think most people are aware that there is an increasing move among the pediatric community with young children, perhaps between six months and two years of age, receiving influenza virus vaccines. Not recommended but "encouraged" at the last meeting of ACIP.

This whole question of whether children would be naive to a strain, if we got Victoria-like strain in this year and there is indeed an enhanced use of vaccine among the pediatric population, particularly the young susceptibles, this might indeed abort some of the concerns you have about their not having previous experience not in 2002/03 but 2003/04 comes around and with the unpredictability of influenza patterns, that may save us some grief. Anyway, I vote yes.

DR. DAUM: Thank you. So you concurred and conferred.

DR. KATZ: Thank you.

DR. DAUM: Dr. Kohl.

DR. KOHL: I concur with Dr. Couch but I'm uncomfortable with the (inaudible).

DR. DAUM: You want to go on record stating why?

DR. KOHL: I would, I guess, reinforce a comment that Dr. Couch made in terms of really needing some more research on children and on everybody with quadravalent type thing if we get in the situation again.

DR. DAUM: Thank you.

Dr. Markovitz. Maybe we can recover Dr.

Markovitz later.

Dr. Overturf.

DR. OVERTURF: I hope I'm not on mute. Am I on mute? Can you hear me?

DR. DAUM: I hear you fine.

DR. OVERTURF: I would concur also. I agree that I'm uncomfortable with that mostly because I think we need additional research in the quadravalents actually. I think there are no options this year and the one that's been outlined is fine.

DR. DAUM: Thank you.

Dr. Palese.

DR. PALESE: Yes, I concur with Dr. Couch.

DR. DAUM: Dr. Parsonnet was not here before.

DR. PARSONNET: No, I'm here.

DR. DAUM: You are here now?

DR. PARSONNET: Yes.

DR. DAUM: Good. Welcome.

DR. PARSONNET: I've been here all along. I let my crystal ball at home today but in the absence of that, I guess I concur with the rest.

DR. DAUM: Thank you very kindly.

Dr. Poland.

DR. POLAND: I concur but would like to go

on the record as saying because we've been saying it for so many years that, No. 1, we do need pediatric sera and have pediatric subjects involved. No. 2, at some point we really do have to give serious consideration to the idea of quadravalent vaccines.

DR. DAUM: Thank you very much.

Dr. Snider. Dixie, are you there?

DR. SNIDER: I'm here, Bob. I concur with what Bob Couch has said and would also add my voice to those who have called for the solution to the issue of trying to make the best public health decision and get the coverage under conditions of uncertainty like this in which we have two candidates, B lineages, that ideally we would like to cover but for reasons of feasibility, regulatory, and so forth.

We don't apparently have the ability to do that, but I think we do need to find a way around that. I also concur with what Steve Kohl said and Bob Couch said and others about the importance of the data for children.

DR. DAUM: Thank you, Dixie.

David Stephens.

DR. STEPHENS: Uh, yeah. I think there is increasing evidence for B/Victoria. I think I concur with No. 3 and Bob Couch's comments.

DR. DAUM: Thank you very much.

Dr. Whitley.

DR. WHITLEY: I support Bob's recommendation.

DR. DAUM: Thank you very much.

Perhaps least, and certainly last, I also think that B/Victoria is the way to go here, but I'm also mindful of the comments and just want to go on record reinforcing them. The pediatric issues that have been raised, the research that needs to be done to establish how to make an additional valent vaccine should it be desired again in the future.

My annual plea for studying people who get influenza despite being vaccinated to try to understand why that's so. I think a very small contribution for each dose that's sold might help support some of that work which is badly needed.

DR. SACHS: Hi. This is Jody Sachs from the FDA. I just wanted to ask three people if they were present to go ahead and vote. Dr. Markoff -- Markovitz. I'm sorry. Is he present? Okay. Dr. Kim.

DR. KIM: I support Dr. Couch's recommendation.

DR. SACHS: Thank you. There's one more

person. Dr. Faggett.

DR. DAUM: Dr. Faggett is not on and Dr. Markovitz is not on.

DR. SACHS: Okay. We're good. Thank you.

DR. PALESE: This is Peter Palese. Could I just make one other comment on the record?

DR. DAUM: Go ahead.

DR. PALESE: I would like to see some utilization of tests as well. I would like to know how good these antisera are in terms of utilizing virus not only in terms of hemagglutination inhibition and that goes along with more research which some of our members have supported.

DR. DAUM: Thank you very much.

I would like to bring this Session 1 now to a close and thank Drs. Couch, Dowdle, Eickoff, and Poland for their participation. I would also like to propose that we have a five-minute no hang-up break for those that need to run out to the potty and then we'll continue at exactly 1:30 central, 2:30 eastern.

Steve, I don't know what that makes you.

DR. KOHL: Bob, I'm not going to be part of the second session. I want to say goodbye to you all.

DR. DAUM: Okay.

DR. SACHS: Thank you.

DR. DAUM: Five-minute break.

DR. SACHS: Five minutes.

(Whereupon, at 2:25 p.m. off the record until 2:34 p.m.)

DR. DAUM: Thank you Roland. Thank you, Dr. Katz.

DR. MIDTHUN: Hi. This is Karen Midthun. Can I just make one last comment on the influenza? I just wanted to say that we do take the input of the committee to heart with regard to the influenza and that we will be working with CDC and with NIH to see how we might be able to address some of those issues that have been raised with regard to obtaining additional studies and sera, etc. Thank you.

DR. DAUM: Good feedback, Karen, for the committee to have. We ramble on sometimes with these recommendations but we hope someone is listening and, best of all, that there be action such as what you described.

DR. MIDTHUN: We are.

DR. AGUILAR-CORDOVA: This Estuardo Aguilar-Cordova.

DR. DAUM: Hello.

DR. AGUILAR-CORDOVA: Can you hear me?

DR. DAUM: Yes.

DR. AGUILAR-CORDOVA: I'm new to this and I just wanted to get a little bit more information. I've heard a lot of discussion about the quadravalent and trivalent and the 7.5 micrograms versus 15 micrograms. What I wasn't quite clear is what happened and what the data is or has been discussed as far as the amount and the affect of the change from 15 to 7.5. Given all the discussions about the number of doses that might be available, I have just a quick comment on whether 15 micrograms has been settled as the standard and does that have to be?

DR. DAUM: What the committee said was that 15 micrograms remains our standard but we base that upon comments that were offered by experts at the beginning. Perhaps FDA folks or CDC folks want to make one comment about this but then we really must move on.

Roland or Nancy, are you still there?

DR. COX: Roland, I think it's more of an FDA issue.

DR. LEVANDOWSKI: Right. Dr. Midthun may be able to help me out here also. What we said at the beginning was that current vaccines have been standardized to 15 micrograms of each of the

hemagglutinins that are contained. I think all the information that we have from modern influenza vaccines comes from vaccines that have contained 15 micrograms of each of the HAs.

To change that formulation, the expectation is that there would need to be some type of clinical studies to indicate both the safety and the efficacy of the vaccine. That would be the same as what we would be looking at for any other kind of vaccine.

DR. MIDTHUN: Right. I guess to summarize it, it would be very, very difficult, really impossible, to get the type of clinical data assembled in time for this year to actually get a quadravalent preparation available. I think we did hear a lot of input that it would be very desirable to try to generate data so that in the future we would have data that would be able to address this issue.

DR. DAUM: -- gone over but I agree with Dr. Aguilar-Cordova that this is an area that we need to think about some more and have more input on.

Let's now move to Session 2 proper. Jerry Weir, are you there?

DR. SACHS: This is Jody from the FDA. I would just like to state that Dr. Weir, Dr. Feinstone,

and Dr. Markoff are present and they are ready to go for Session 2. Dr. Lemon is on the call ready to go also. Thank you.

DR. DAUM: Thank you very kindly. With that, I'll again call on Dr. Weir for the overview of the Division of viral products.

DR. WEIR: Hi. This is Jerry Weir from the Division of Viral Products. Can everyone hear? Okay. For the remainder of this session we are going to review the site visit report for the Laboratory of hepatitis Viruses and vector-borne viral diseases.

This site visit took place on November 6, 2001. What I'm going to do is just give a very brief overview of the Division of Viral Products. I think most of you may have a handout to follow along.

The Division of Viral Products is one of three division in the Office of Vaccines, Research, and Review. At the present time I am the acting director of the division. Delores McVitty is the acting deputy director of the division.

There are seven laboratories in the Division of Viral Products; the Laboratory of hepatitis Viruses, the Laboratory of Vector-Borne Viral Diseases, and the Laboratory of Retrovirus Research, the Laboratory of DNA Viruses, the

Laboratory of Pediatric and Respiratory Diseases, the Laboratory of Immunoregulation, and the Laboratory of Methods Development.

As I said earlier, the site visit focused on the review activities of two of these laboratories, that of the Laboratory of hepatitis Viruses, and the Laboratory of Vector-Borne viral diseases.

In general, the mission and the functions of the -- I'm sorry. Go ahead.

DR. DAUM: Dr. Weir, are you there?

DR. SACHS: Yes. Go ahead, please.

DR. WEIR: I'm still here.

DR. DAUM: Good. Go ahead. I think Ms. Fisher just joined.

DR. WEIR: Okay. I'll continue. I was about to talk about the overall mission and functions of the Division of Viral Products. Briefly we have research efforts and review responsibilities. The laboratories and the research efforts in the different laboratories focus on a variety of topics and they include viral pathogenesis, vaccine development evaluation, viral vector evaluation, as well as vaccine safety and efficacy.

In general our review responsibilities mirror those research efforts or the research efforts

support the review responsibilities. In all of our laboratories we have responsibilities for the review of investigation of new drug applications, biological license applications, as well as we're responsible for the release of viral vaccines and numerous post-marketing activities.

The Division of Viral Products has a full-time staff of approximately 67. A total staff, however, is over 100, about 110 as of today. This is mostly because of post-doctoral fellows that are brought into the division on soft money.

Since the site visit committee met, however, we now have a potential increase in FY 02 of more than 10 full-time staff members as a result of counter-bioterrorism efforts for this year. The budget for FY 02 is approximately at this time about 1.1 million. When the site visit committee met in November the figures for this year were not available.

This 1.1 million represents about the same budget as last year and this is an increase. As I pointed out to the site visit team at that time, this is an increase over a low of $750,000 to $800,000 in operating funds in FY 99 and FY 2000.

We also, as I pointed out at that time, we have supplemental funding from outside sources which

now equals or is greater than our internal operating funds. This is a reflection on the success of most of our, or all of our, laboratory programs.

As I mentioned a minute ago, we have potential increases in staff due to counter-bioterrorism this year. We also have increased funding this year that will become available because of the bioterrorism initiative.

The two laboratories that review in November were the Laboratory of hepatitis Virus Research. Research in that laboratory focuses in general on the immunobiology of hepatitis C and strategies for vaccine development.

The major regulatory responsibilities of that laboratory are in the regulation of hepatitis virus vaccines. This, of course, includes other hepatitis viruses other than just hepatitis C.

In the Division of Viral Products, Laboratory of Vector-Borne Viral Diseases, the research efforts mostly focus on mechanisms of replication and pathogenicity of vector-borne viruses and also strategies for vaccine development.

The regulatory responsibilities of this laboratory include the regulation of vaccines for vector-borne virus diseases, as well as hepatitis A

and rabies.

On November 6, 2001, the site visit committee met to review the progress of the programs of the research programs in these two laboratories and they evaluated individuals in these two laboratory programs for their progress and assessed the future directions of where these two programs were going.

Briefly that is the overview and I'm going to go back on speaker phone now as we turn to -- before we turn to Dr. Feinstone.

DR. DAUM: Thank you very much, Dr. Weir. Are there committee questions or comments for Dr. Weir?

DR. KATZ: This is Sam Katz. I have one question. Why is hepatitis A virus in the vector-borne lab instead of the hepatitis Lab?

DR. WEIR: That goes back several years. Dr. Feinstone may tell you more but there was a potential conflict of interest because Dr. Feinstone was one of the co-discoverers of hepatitis A.

DR. DAUM: Thank you. Dr. Weir, I have a question. The FY 02 budget of approximately $1.1 million, that I presume does not include salaries of those working there.

DR. WEIR: That's correct. I was only

referring to operating funds.

DR. DAUM: How much of those are earmarked for the research operation?

DR. WEIR: Well, that is essentially our research operating budget. That also includes the overhead for the division itself but essentially that is our research budget.

DR. DAUM: Other committee questions or comments? Good. Then let's go on to hear from Dr. Stephen Feinstone regarding the synopsis of the Laboratory of hepatitis Virus.

DR. FEINSTONE: Good afternoon. This is Steve Feinstone. I'm going to present the program of the hepatitis Lab. The hepatitis Lab was begun in 1989 and continued through this time.

Originally we had two groups within the laboratory, a hepatitis A group and a hepatitis C group. In recent years the hepatitis A group was headed by Gerardo Kaplan who has now moved to the Office of Blood where he has taken a position as a lab chief.

Presently we have just the one group in the hepatitis Laboratory that's focused primarily on hepatitis C. We have seven members in the laboratory now, myself and six other individuals. Marion Major

is a visiting scientist. Deb Taylor is a staff fellow. Montserrat Puig is Oakridge fellow. Kathleen Mihalik and Peter Thompson are biologists. Recently Tonya Orin from Australia has joined the laboratory and is a Fogerty fellow.

The laboratory has regulatory responsibility for all the hepatitis viruses including hepatitis A, B, C, and E. We have no -- we've had no applications dealing with hepatitis D or Delta.

We are involved in the regulation of hepatitis A. As Dr. Weir explained, I have a conflict of interest so I personally do not deal with hepatitis A but Marion Major in our laboratory does do review work for hepatitis A.

In recent years Dr. Markoff has been very active in review hepatitis A vaccine applications, especially during the clinical reviews which is the major part of the review work. However, those applications were also handled in the hepatitis Laboratory by Dr. Kaplan.

As I said, we have applications and regulatory work in all the major hepatitis viruses except for hepatitis D. We also function outside the office. I frequently am called on for consultations by the Office of Blood or the Office of Therapeutics.

Debra Taylor, who is very knowledgeable in interferon, has been working with individuals in the Office of Therapeutics on interferon applications. I think that is most of our outside the office work.

From the research point of view, as Dr. Weir pointed out, our major focus has been in the area of the immuno-biology of hepatitis C. We have a major program to study the immune response in using chimpanzees that are inoculated with a monoclonal form of hepatitis C virus that was derived from the infectious HCV CDNA clone developed with Charlie Rice's laboratory now at the Rockefeller.

Using that material, we studies immune responses in chimpanzees in what we hope is a very controlled way. This is work that is largely sponsored by an NCI grant which I'm co-principal investigator with Charlie Rice. As I said, that is the major project in the laboratory right now.

In addition to that, Dr. Taylor has initiated a program to study mechanisms of interferon resistance to hepatitis C virus. We are also working actively now on trying to develop small animal models for hepatitis C that will hopefully reduce our dependency on chimpanzees.

The details of the program are presented

in the briefing book. Beyond what we do in the laboratory we also have major collaborations with various groups both in the intramural community at NIH and extramurally we work very closely with Charlie Rice's laboratory, with Harry Greenberg in the extramural program.

Intramurally we work with Jake Liang, Barbara Rareman, Jay Rasophski, and Curt Harris. We also have a lot of cooperations with Mei Ying Yu and the Office of Blood.

I think that generally sums up the program.

DR. DAUM: Are there questions or comments from committee members for Dr. Feinstone? If not, we'll say thank you very kindly and ask for Dr. Markoff. Hopefully he's here.

DR. SACHS: Yes, he's here and ready to go.

DR. DAUM: He's here and ready to go to give us a synopsis of the Laboratory of vector-borne viral diseases. Dr. Markoff.

DR. MARKOFF: Thank you very much. Thank you members of the committee for being present.

I hope everybody received the three slides that I sent out late last week. In the first of those

slides you can see an overview of the organization of the laboratory and I'm going to say a few words about that.

You might note on the slide that the LDVD includes the electron microscopy staff which consist of Dr. Jackwell and Muller and biologist Marilyn Linguist. The EMS, as I call it, was not reviewed during the recent site visit because they have more or less a regulatory function.

In addition to the EMS, then the laboratory consist of five FTEs and that would include myself, staff scientist Dr. Barry Falgout, Senior Staff Fellow Dr. Robin Levis, and Microbiologist Janet Burn and Stephanie Polo.

Currently in the Laboratory we also have an Oakridge fellow, Dr. Li Yu, and a guess worker Dr. Eileen Kelly who is on loan to us from Walter Reed Army Institute of Research. This is a total of seven investigators in the lab at the moment excluding the EMS.

LBD reviews all the submissions related to vaccines for the prevention of vector-borne virus diseases. This includes the licensed vaccines YF-vax, which is the yellow fever vaccine licensed in this country to Adventist Pasteur and JE-vax. Those are

vaccines for yellow fever and JE respectively, of course.

These are both flavi virus pathogens. Other flavi virus vaccines under development include novel JE and yellow fever vaccines, mono and tetravalent Dengue vaccines, and vaccines to prevent illnesses caused by tick-borne encephalitis and West Nile viruses.

LBD also reviews vaccines related to the new world alpha viruses such as Venezuelan, Western, and Eastern Equine encephalitis viruses. Additional victor-borne virus pathogens are targeted for vaccine development and the list includes some of the arena viruses such as Lhasa fever and Junin viruses and philo viruses such as E-boli and Marburg. We don't have any applications for the latter viruses at the moment, however, but these would also fall under our purview.

LBD has also reviewed responsibility for rabies, all rabies, and hepatitis A vaccine submissions as Steve and others have described. Dr. Levis is primarily responsible for ishes related to rabies vaccines.

Robin has taken the lead on behalf of OVRR in an international effort to claim the potency test

for lot release of rabies vaccines for one based on a leaf of mouse challenge to one based on ELISA. She also contributed to the CBER team biologics program as a lecturer and is one of the few, if not the only, staff fellow to have served as an expecter of manufacturing facilities.

Dr. Falgout has distinguished himself as a reviewer of manufacturing protocols in all areas and he serves as a consultant to the Office of Therapeutics in CBER on submissions related to adenovirus vector gene therapy. Barry is the only scientist in CBER with previous experience as an adeno virologist. As was mentioned, the review of the clinical submissions related to hepatitis A vaccines has been my responsibility.

The scientific effort in our lab centers around the creation of infectious DNA for positive strand RNA viruses using various flavi viruses as models. It is also currently possible to create infectious DNAs for negative strand RNA viruses if preliminary gene function is supplied in trends.

The use of infectious DNA and RNA virus vaccine development is quite attractive because site directed mutagenesis of the viral gene on this facilitated and issues related to tissue culture

passage that predate DNA cloning are abrogated. In other words, the vaccine is safer if it comes from an infectious DNA.

The major portion of the support for our research effort comes from the Walter Reed group under an IAG in which we have agreed to create infectious DNAs for each of their existing tetravalent set of attenuated Dengue viruses that were initially created by serio passage of human virulent Dengue viruses in primary dog kidney cells. This effort is led by Dr. Falgout in our lab.

This is one example of the use of infectious DNAs to enhance vaccine safety. In a similar vane, Dr. Falgout has also created an infectious DNA copy of a live attenuated JE vaccine strain SA/14/142. That vaccine is used widely and successfully in China to immunize hundreds of millions of children against JE but it would likely be unacceptable for licensure outside China due to its history of both attenuation and manufacture in primary hamster kidney cells.

We also use the infectious DNA technology in our basic science projects and here is a short list of examples. The first one would be that in a recent set of experiments Barry discovered that punitive

full-length DNA copy of the JE vaccine virus genome was infectious despite the fact that it lacked the three prime terminal six nucleotides of the RNA.

RNA isolated from the resulting replication competent virus was shown to contain the missing six nucleotides indicating that by some unknown mechanism they had been restored. This set off a chain of experiments using our Dengue-2 infectious clone which was easier to work with than under BL-2 conditions. We were able to demonstrate that any number of deletions up to about seven nucleotides can be deleted from the three prime end of the DNA and these are restored.

This is evidence for an unknown function probably of the viral RNA preliminaries and/or cellular proteins to actually restore missing nucleotides from the three prime end of the genome which will alter the current concept of how this RNA replication proceeds with the virus.

The second example would be that in 1998 we published a study of a conserved and thermodynamically stable stem-leuc structure formed by the three prime terminal 90 nucleotides of the flavi virus genome by site directed mutagenesis of that domain and the Dengue-2 genome.

One of those mutant viruses derived in that study which we call mutant F, just because it came after mutant E, had a host range phenotype in that it replicated only to very low titres in mosquito cells but proved very well in monkey cells.

We introduced that mutation into a human virulent Dengue-1 virus genome and showed that this mutant was highly attenuated in monkeys. Interestingly, it also displayed the same host range restricted phenotype so we are developing a tetravalent set of mutant F viruses as vaccine candidates.

Finally, Dr. Levis demonstrated several years ago actually that the function of one of the key viral nonstructural proteins, and this one could be complimented in trends, if a viral genome with a large in-frame deletion of NS-1 gene sequences was introduced into cells constituatively expressing it as one.

Robin went on to demonstrate that NS-1 probably protects virus infected cells from apoptosis and that yields of infectious virus from NS-1 expressing cells, and this is even wild-type viruses, are, therefore, increased and we feel that this finding could be useful in eventually manufacturing of

any Dengue vaccines.

Those are just three examples of how we apply some basic science congruent with the mission of CBER.

DR. DAUM: Interesting issues. Committee comments or questions for Dr. Markoff?

DR. KATZ: Sam Katz with a question about Dengue. Where are we as far as development of Dengue virus vaccines are concerned?

DR. MARKOFF: There are a number of vaccines under development by different companies. I don't know what I can say about it. I really can't say anything. This candidate vaccine that has come from our research was just a fortuitous event. Of course, we don't have the wherewithal, the facilities, the funds, or even the desire to be vaccine manufacturers. That particular mutant virus has been patented. That's all I can say.

DR. KATZ: Thank you.

DR. DAUM: Other questions or comments for Dr. Markoff? Okay. With that we will move into open public hearing for Session 2.

MS. SACHS: I'd like to ask -- this is Jody Sachs of the FDA -- if anyone present would like to speak. There is no one in the room where I am

right now that is asking to speak. Thank you. I'm going to at this time turn it back to you, Dr. Daum.

DR. DAUM: Would you like to have a break before we move into closed session, Jody, or can we just go right in?

MS. SACHS: What we need to do is just give me one minute to clear the room and I'll start to ask the people that need to get off get off if you would like me to -- the few people that need to hang up, I will be happy to do that.

DR. DAUM: So we'll meet at 3:05 eastern. Will that be enough time, Jody?

MS. SACHS: Yes. That sounds very good. Thank you.

DR. DAUM: We'll go into Session 3 at 3:05 eastern.

MS. SACHS: Sounds good. Thank you.

(Whereupon, at 3:02 p.m. off the record until 3:06 p.m.)

MS. SACHS: Hi. This is Jody from the FDA. I just wanted to ask if Dr. Couch, Dr. Dowdle, Dr. Eickoff, Dr. Poland are still on the line, it is now time to -- okay. We're fine, Dr. Daum. We just did with the operator. We're fine. We can go ahead.

DR. DAUM: Good. Then let's hurdle along

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CLOSED SESSION

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: March 6, 2002

Place: Bethesda, MD

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