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FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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MEETING

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FRIDAY

MARCH 9, 2001

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The Committee met at 8:00 a.m. in the Versailles Room of the Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Robert S. Daum, Acting Chair, presiding.

PRESENT:

ROBERT S. DAUM, M.D. Acting Chair

CLAIRE BROOME, M.D. Temporary Voting Member

JAY BUTLER, M.D.

NANCY COX, Ph.D.

MICHAEL DECKER, M.D.

PAMELA S. DIAZ, M.D. Member

THEODORE EICKHOFF, M.D. Temporary Voting Member

WALTER L. FAGGETT, M.D. Member

PRESENT (Continued):

JUDITH D. GOLDBERG. Sc.D.	Member
DIANE E. GRIFFIN, M.D., Phd	Member
CAROLINE HALL, M.D.	Temporary Voting Member
SAMUEL L. KATZ, M.D.	Member
KWANG SIK KIM, M.D.	Member
STEVE KOHL, M.D.	Member
DOLORES LIBERA	
PAMELA McINNES	
NANCY CHERRY, Executive Secretary	

I-N-D-E-X

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

(8:15 a.m.)

ACTING CHAIRMAN DAUM: Good morning. Could everybody take their seats and get ready to do our business, please.

This is an open session, Number 8, of this meeting. I think we will begin by asking the Committee members to introduce themselves, and then we will turn the floor over to Nancy for a conflict of interest statement. Dr. Kohl, will you tell us who you are?

DR. KOHL: Steve Kohl, Oregon Health Sciences University.

DR. KIM: Kwang Sik Kim, Johns Hopkins.

DR. GRIFFIN: Diane Griffin, Johns Hopkins.

DR. DIAZ: Pamela Diaz, Chicago Department of Health.

DR. KATZ: Yesterday I was Sam Katz. I guess I'm still Sam Katz from Duke University. How many times do we introduce ourselves?

ACTING CHAIRMAN DAUM: We are glad to hear that.

DR. GOLDBERG: Judy Goldberg, New York University.

DR. COX: Nancy Cox, CDC, Atlanta.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. BUTLER: Jay Butler, CDC.

DR. HALL: Caroline Hall, University of Rochester.

MS. LIBERA: Dolores Libera, Allergy and Asthma Network/ Mothers of Asthmatics.

DR. McINNES: Pamela McInnes, National Institute of Allergy and Infectious Diseases, NIH.

DR. DECKER: Michael Decker, Aventis Pasteur and Vanderbilt University.

DR. LEVANDOWSKI: Roland Levandowski, Center for Biologics.

ACTING CHAIRMAN DAUM: And I am Robert Daum from the University of Chicago.

We now will turn the floor over to Nancy Cherry for a conflict of interest statement regarding today's matters.

MS. CHERRY: And today it is brief. The following announcement addresses conflict of interest issues associated with sessions 8 and 9 of the Vaccines and Related Biologics Products Advisory Committee meeting on March 9, 2001. These sessions focus on completing the formulation of the influenza

virus vaccine for the 2001-2002 season and on activities within two laboratories of FDA.

The Director of the Center for Biologics Evaluation and Research has appointed Doctors Broome, Eickhoff and Hall and temporary voting members for the discussion on influenza. Based on the current agenda, it has been determined that these committee discussions present no potential for a conflict of interest.

That's it.

ACTING CHAIRMAN DAUM: That's a remarkable statement, I must say, in my experience here. Thank you, Nancy.

We will now consider the first issue on today's agenda, which is the completion of the formulation of the influenza virus vaccine for next year that the Committee initiated at its last meeting.

For a review of the current situation, we will call on Roland Levandowski of the FDA to initiate this discussion.

DR. LEVANDOWSKI: Thank you, Dr. Daum. Good morning, everybody. Welcome back. It hasn't been so long since we were here before discussing influenza. I know that some of the members on the Committee today weren't here in January. So I will do

a brief review of information that we went over and then try to bring you up to date on what's happened in the interim.

In January, using the information that was then available, the Committee made some preliminary recommendations for the composition of influenza virus vaccines to be used in the United States during the upcoming 2001-2002 influenza season.

The information that was available at that time, which was presented by a number of sources, indicated that influenza A(H1N1) and influenza B viruses were predominant in most parts of the world and the United States, and that relatively few influenza A(H3N2) viruses were being found.

The vast majority of the influenza A(H1N1) strains were very closely related to the current vaccine strand, which is A/New Caledonia/20/99, but a few of the strains were similar to an older vaccine strain, A/Johannesburg/82/96. Those have continued to appear over the last few years and don't appear to pose any particular problem, since we had seen in the past that the New Caledonia vaccine produces antibody responses that cover those strains quite well.

The few influenza A(H3N2) viruses that were being recovered in the United States and

elsewhere were, for the most part, similar to the current vaccine strain, which is A/Panama/2007-99.

The influenza B viruses being identified were all of the B/Yamagata/1688/HA lineage, and that included many related to the current vaccine, which is B/Yamanashi/166/98. But the majority of the strains were divergent, and they were really more similar to the B/Sichuan/379/99 reference strain.

There were very few B/Victoria/02/87 HA strains being identified, and we are all wondering whether that particular lineage is now going to die out or whether it will persist in some little niche somewhere.

Serologic data from people who had been immunized with the current vaccines indicated that the H1N1 viruses and the H3N2 viruses would be expected to be pretty well covered by the current vaccine.

For the influenza B viruses, however, there was evidence that suggested that the current vaccines would not provide the best match with most of the circulating strains and, although there were reductions in antibody responses to the new influenza B viruses seen in serologic testing, those reductions were actually on the moderate side. But they seemed to be pretty consistent, even though they weren't seen

in every one of the tests that was done.

An additional concern about the influenza B strains was whether it would be possible to find a strain that is suitable for large scale manufacturing. We heard somewhat mixed messages from the manufacturers regarding the strains that had been examined at that time.

We were told that many of the possible influenza B candidate strains were very poorly growing, and they would be expected to give yields that were so low that manufacturing would be very difficult on a large scale basis.

Although the B/Victoria/504/2000 strain, which is a B/Sichuan/379/99-like strain, appeared to grow well, on manufacturer who maybe through his Liverpudlian accent didn't come across that clearly, but he noted that the yield through the entire process had been somewhat disappointing in their experience.

It was also noted that the other B/Sichuan-like strain that has been used for manufacturing for the Southern Hemisphere during this last campaign, the B/Johannesburg/599 strain, was a very low yielding strain and definitely would not, in its current form, be acceptable for large scale manufacturing.

As a result, the Committee recommended that the H1N1 strain in the vaccine should remain as the A/New Caledonia/20/99 and that, in the absence of any new data that might alter the recommendation, the H3N2 strain in the vaccine should remain as an A/Panama/2007/99 strain and, again in the absence of any data, that the influenza B strain for the vaccine should be changed to a B/Sichuan/379/99-like virus, and many of the members focused on the B/Victoria 504/2000 strain as the most likely candidate.

In the interval between January and today, the World Health Organization made its recommendations for vaccine composition and, not surprisingly, they have recommended an A/New Caledonia/20/99(H1N1) strain, an A/Moscow/10/99-like(H3N2) strain, which really means the related -- the closely related A/Panama/2007/99 strain that has already been widely in use around the world, and a B/Sichuan/379/99-like strain.

There was a notation in the WHO recommendations that both B/Johannesburg/599 and B/Victoria/504/2000 have been used for preparing vaccines for the Southern Hemisphere.

Those WHO recommendations were made with information that was updated from what we had

presented here, and that's what we would like to do this morning. We would like to bring to the attention of the Committee for its consideration.

We do have a question, but it's sort of a question that the answer will be probably immediately obvious or immediately apparent: Based on the updated information that we are going to present today, would the Committee make any changes in recommendations that were provided in January for the composition of the influenza virus vaccines to be used in the U.S. in 2001-2002?

I think we know the answer to that question already, but we would like to give you the opportunity to answer it.

ACTING CHAIRMAN DAUM: Thank you very much. Dr. Cox, would you like to give us additional surveillance and epidemiology information?

DR. COX: Good morning. It's very nice to be on the -- in the final stages of what is for us a three-part process in terms of vaccine recommendations, first of all, the January meeting here in Washington, then the WHO meeting in Geneva in February, and now once again in Washington.

I should mention that for the meeting in Geneva we really have a lot of additional information

that's presented -- that's brought to the table by other WHO collaborating centers. There has, over the past ten years, been an increase in the amount of data that is being generated globally, and I think that meeting in Geneva is extremely important to bring the whole global context into perspective.

So having said that, we will go ahead and look at the data that we have for the season in the United States, an update compared to what you had last time, and also we will go over some of the virus characterization that's occurred since we last met.

As Roland just said, this year we have had predominantly influenza A(H1N1) and influenza B viruses being isolated. The B is represented here in green. Actually, the proportion of isolates that are influenza B is increasing as we go through the season.

It appears that the season -- It appears from this index of activity that the season peaked in about week 4, the last week in January, and we had a percent positivity for influenza of respiratory specimens that were submitted of 24 percent, and this compares as being a bit lower than some of the percentages we've seen in the past which had ranged up to 33 percent at the peak of previous seasons.

Overall, about 13 percent for the entire

season, overall about 13 percent of the specimens were positive for influenza.

This year over 30 percent of the influenza A's have been subtyped, and we have really only had sporadic cases of influenza H3N1, and you can see them barely represented here. Next slide.

When we look at pneumonia and influenza mortality peaks for the past years, and we remember back to what was going on, we can see very substantial peaks associated with the last four influenza seasons. Those were all seasons that were dominated by H3N2 viruses.

This year, when we have had relatively little or very little H3N2 activity, we haven't had the percentage of deaths that are attributed to pneumonia and influenza go above the baseline in any week. So it's really been a very mild season when you look at this particular index.

Likewise, when we look at the percentage of visits for influenza-like illness in our Sentinel Physicians Network, peak activity occurred during weeks three, four and five, I think, and the percent of visits for influenza-like illness peaked at about four percent. That compares with five or six percent in past years when H3N2 viruses have circulated.

If we look at the weekly assessment of influenza activity as reported by state and territorial epidemiologists, we can see that, again, peak activity occurred in around weeks four and five, and that widespread activity was reported by fewer states than in previous years.

We still have four states reporting widespread activity, but this index is certainly in decline as well. Next, please.

So the season has been very mild and is declining and, although the proportion of influenza B isolates is increasing in some areas of the country, we are really not seeing increases of influenza activity associated with the increasing proportion.

Now I am going to go on to the virologic surveillance, and this is just an update of H1N1. I just wanted to demonstrate that we had actually looked at a number of additional viruses, about 100 additional H1N1 viruses, and we are seeing the same picture that we saw before. That is to say, the viruses are really New Caledonia-like.

As Roland mentioned, we are seeing some of the Bayern or Johannesburg-like strains, but they are in the minority, and we are not concerned about these, because they appear to be well covered by the vaccine.

Then we are seeing just a very small proportion of viruses which are reduced in titer to the New Caledonia strain, and this would be expected, and this is what we were seeing before. So even with additional information, there's nothing really new. Next, please.

Now we are going to move on to the H3N2 viruses. There was a lot of discussion about H3N2 and, of course, we really want to make sure that we don't miss anything important, because these viruses do cause the most severe morbidity and are responsible for mortality.

I'll just spend a moment orienting you to this particular slide. We have here the old Sydney strain, the old vaccine strain, and then here we have Moscow/10, which is the recommended strain, Panama, the strain that was in last year's vaccine, and then we have a series of additional viruses and their antisera.

What we were seeing at the meeting in January, at the end of January, and what we are continuing to see is that the viruses that are -- the H3N2 viruses that are being isolated now are very well inhibited by antisera to all of these reference strains.

The viruses are looking very homogeneous, and they are very well inhibited even by antiserum to the old Sydney vaccine strain.

Here we have viruses from the U.S., one from Europe, and then some strains from Korea. We were most interested to see if any of the strains that we could get our hands on from Asia might look different. The bottom line is none of the strains looked different. Next, please.

We also received two influenza H3N2 viruses from China. They are not very new strains. In fact, one was isolated in May, the other in July, but just to be sure that we weren't seeing anything new at all, we put them into ferrets and developed ferret serum to these and put the ferret sera into these tests.

Here we have some strains from December and January. We have strains from the U.S., from Asia. We have a number of recent Korea viruses that came through to us through the military surveillance that is going on in Asia, and then these two strains that were isolated in November from Thailand.

As you can see, there is really nothing different at all. So this was actually very reassuring to us.

There was a great deal of discussion at last January's meeting about the neuraminidase, of the N2 neuraminidase. That is the neuraminidases of the Panama-like viruses versus some other strains.

We had developed some data at that time, but it was rather preliminary, and I really didn't want to discuss it in detail until we had been able to repeat our test results a number of times.

We knew that genetically the neuraminidase of the Panama vaccine strain was different from the neuraminidases of the majority of strains that were circulating, but we didn't know if this would translate into an antigenic difference, and there was concern expressed by Dr. Kilbourne and others.

So this is the test that we did. We did a number of tests, and they were all consistent, but this is the test that was done very recently, actually, at the beginning of this week. Here we have ferret antisera to Panama, specific rabbit serum that was made against a reassortant which has an irrelevant hemagglutinin, but the neuraminidase of the Panama strain.

This perhaps is the most interesting antiserum to look at, because you are interested in determining whether you can detect differences in the

way this antiserum inhibits some of these viruses that have the neuraminidases that are in the different genetic groups.

We have down here just as a control virus the Bangkok/179. We have a good rabbit serum, or relatively an okay rabbit serum to that virus. We would certainly expect to see fairly dramatic differences between this 1979 strain and the strains that are isolated in '99 to 2000.

What we can see is that we really don't have -- we don't have differences that we can really detect here. So this was very reassuring to us, that we don't need to be concerned about the neuraminidase of the Panama strain. Next, please.

This is just to demonstrate that we had analyzed additional viruses since our last meeting and that all of them are Panama-like. I think we can move on to influenza B viruses now.

There has been a lot of influenza B activity worldwide, and at our last meeting we were particularly interested, and there was a certain amount of discussion about viruses that we had received from China and whether these viruses would look like B Sichuan or whether they would have moved on.

We have a number of antisera here. I'll just spend a minute orienting you. This is the Beijing/184 recommended B strain. This is the Yamanashi actual vaccine strain, and then we have a variety of strains here, C, D, E and F, which are considered to be Johannesburg-like and which had been explored by the manufacturers as possible vaccine strains for use.

On the right here we have an antiserum to Beijing/243, which represents the old Victoria lineage. I think at the time of our previous meeting, we really had not seen viruses on the Victoria lineage anywhere, but now we have four viruses that have been submitted from the National Influenza Center in Hong Kong that are Victoria-like, and they are represented here by the last two antigens on this table. You can see that it's very easy to distinguish the Victoria and the Yamanashi lineages of viruses.

I would just like to mention that, similarly to what we were seeing in January, many of the current viruses are not well inhibited by antiserum to the Yamanashi virus, and that they are better inhibited by antisera to Johannesburg, Sichuan/379, Victoria/504 and this Japanese strain, Shizuoka/480.

The viruses from China that are represented here by antigens 19 through 24 -- from mainland China, I should say -- look, generally speaking, Sichuan-like, although there are occasional viruses which are not as well inhibited, and we are looking into those a bit more. They are, in some cases, low reactors which just are not well inhibited by any antisera.

Here we have a whole series of viruses from the United States, again with the same -- basically, the same panel of antisera. These are relatively recent viruses compared to what you've seen before with isolation dates primarily in January. Again, we can see that the titers are really quite dramatically reduced against the Yamanashi strain and against the Beijing/184 reference serum and that, generally speaking, these strains are much better inhibited by antisera to Sichuan-like viruses. Next, please.

The final B table has some additional data that we'll go over. We have now made ferret antisera against the Guangdong/120 and for two strains which were mentioned by some of the vaccine manufacturers as potentially growing better than some of the other strains. We have confirmed that these antisera to

these strains do inhibit the viruses that are circulating at the current time very well.

We have at the bottom of this table two Chinese strains, B/Wuhan/356 and B/Shenzhen/306, which are less well inhibited by antisera to some of these viruses. This is a phenomenon that we always see. We always have a small proportion of viruses that aren't as well inhibited and, as I mentioned before, we will be exploring these viruses in greater detail as we move on.

My final overhead shows the frequency table that kind of summarizes what we have been seeing, and it's very clear that we have -- that the majority of viruses are better inhibited by antisera to the Sichuan-like strains than to the Beijing and Yamagata-like strains, but some viruses that are circulating still are inhibited by antisera to these strains.

We do have about nine percent, 21 strains, that we consider to be low reactors, and we are exploring some of these strains in greater detail, but the bottom line is that the viruses are Sichuan-like in the main.

I think I'll stop there and entertain any questions that the Committee might have.

ACTING CHAIRMAN DAUM: Questions for Dr. Cox? Dr. Katz.

DR. KATZ: Nancy, on your B viruses on one of your sheets where you have 28 different viruses listed, you have two at the bottom from Hong Kong in 2001 that look to be very little inhibited. Do you have the page that I'm talking about?

DR. COX: Yes.

DR. KATZ: What do those represent?

DR. COX: Those are the Victoria-like strains that I mentioned. There are now four Victoria-like strains that have been isolated in Hong Kong and submitted to us.

Remember, they were circulating in the past in Asia, either -- specifically, in China, mainland China and Hong Kong, and in Japan in the past, but they never actually moved out of Asia into Europe and North America.

DR. KATZ: But they look as if they are not inhibited by B/Sichuan.

DR. COX: No, they are not, and we wouldn't expect them to be, based on historical experience with Victoria-like strains.

DR. KATZ: Epidemiologically, do we expect them to persist or to circulate or that this is the

last dying gasp of those?

DR. COX: We don't know. We have been watching Victoria-like strains circulate in China for the past ten years, and they haven't moved out of China, and they have waxed and waned during that ten-year period.

So the best thing we can do is to keep our eyes on these strains and monitor what's happening. We had actually done an experimental vaccine trial with a Victoria-like strain a few years ago and had developed some data to look at whether or not we would have antibody -- if we immunized people with a Victoria-like virus, would we have antibody against the Yamanashi lineage of viruses.

So we continue to monitor them. If it looks like we need to do experimental trials again, we'll go ahead and get those underway, but it's just impossible to predict if these viruses will die out or emerge.

What we do know is that we have a lot of children who would have no experience at all with this lineage of viruses. So, potentially, they could take off.

ACTING CHAIRMAN DAUM: Thank you. Dr. Kim. Dr. Hall next.

DR. KIM: Nancy, you indicated that there are four states which have a widespread activity in influenza. Do those states have a similar types of spectrum for the viruses being isolated compared to states which have sporadic activities?

DR. COX: Yes. The states that are reporting widespread activity are not the states that are switching to the B predominant. So it looks like continuing activity is independent of this move toward influenza type B circulating in certain areas.

ACTING CHAIRMAN DAUM: Dr. Hall.

DR. HALL: Nancy, I just wanted to say I'm amazed and I always thank you for this wonderful summary. It's really amazing how you've gotten all of this together so logically.

I'm curious, though, about your thoughts on the adequacy of the means of surveillance to detect the import or burden when it is an influenza B year, in the sense that that affects mostly children. I think -- I listen to my colleagues now in medicine who say, gee, it's a mild year, and in pediatrics it's not a mild year.

Part of that may be that the P&I, of course, does not detect as much for children. The other thing, I think, is that even the Sentinel

Physicians and the ones who -- the isolates come more often from adults proportionately or relatively than they do from children, because once people know that influenza is in the community, the pediatricians tend to say, oh, you've got influenza, and don't see them.

So I'm wondering if this really -- As you present it, it's a very mild year, but in terms of the actual burden in health care visits, do you have another way of assessing that than -- Are these milder -- "milder" adult years at least?

DR. COX: Right. The only other way that we have at the moment is to look at hospitalizations after the fact. We don't have an early index of hospitalizations as we do for mortality. But we have been looking at hospitalizations to see if we can pick up more about the burden of disease in other age groups that aren't affected by death.

Then, of course, I think that some of the other surveillance projects that are going on in Rochester and elsewhere will help us understand the burden of disease in pediatric populations better than we do now.

I agree that our indices probably do not pick up burden of pediatric illnesses nearly as well as we would like. So we are going to have to put in

place some new surveillance systems to pick that up.

We do know that we've had a couple of pediatric deaths due to H1N1 and that any influenza virus can affect even a healthy person with death as a result, and these are real tragedies. So we would like not to discount the fact that we know that, even though overall it looks very mild, there are communities that are hit hard, and there are segments of the population that have been hit hard this year.

ACTING CHAIRMAN DAUM: Thank you. Dr. Diaz, please.

DR. DIAZ: I think Dr. Hall brings up a really important point, and from my standpoint it's not only a matter of acknowledging the burden of disease in the pediatric population but also from a surveillance standpoint in terms of the timeliness of identifying flu in a community.

There have been many studies that have shown that influenza in a community usually initiates in the pediatric population, and school absenteeism goes up, and then so on and so forth down the line to adult and elderly deaths. I would just acknowledge that and say, from the standpoint of future surveillance, it would merit us, I think, to look at the pediatric population more carefully and build in

some kind of Sentinel Physician reporting that has a percentage, at least, of pediatric population in that, and to separate that out and use them in a sense for identifying flu when it does come into a community earlier than we typically do.

DR. COX: I should probably emphasize that, in contrast to ten years ago when our Sentinel Physicians were really family practitioners, we now do have a proportion who are pediatricians. So we have broadened the base of our Sentinel Physicians, but we don't analyze our data separately from the pediatricians.

We are really trying to recruit more Sentinel Physicians so that we'll have a robust enough system to start looking at different populations.

ACTING CHAIRMAN DAUM: Thank you. Dr. Katz?

DR. KATZ: I think both Dr. Hall and Dr. Diaz's comments are very important, because those of you who attend ACIP and the American Academy of Pediatrics, Infectious Disease Committee, are aware that there is an increasingly strong movement, particularly if the cold adapted viruses become licensed, to include children in the routine immunization program, not just high risk children but

children, period, with the same thought that Pamela has expressed, that children are frequently the transmitters to adults.

I was surprised to see how much consensus there is to consider children for routine influenza virus vaccine immunization. That, again, may markedly change your epidemiology and your surveillance data.

ACTING CHAIRMAN DAUM: Thank you very much, Dr. Cox, for your usual efficient downloading of much interesting data.

We'll go back to Dr. Levandowski for additional information, serologic results and reference strains, and then options for strain selection.

DR. LEVANDOWSKI: Thank you. In terms of additional information on serologic results, at the WHO meeting, as I mentioned, there was a lot of additional information, and there were serological data that were not previously available the last time we met.

The data that were available in February included more from different sources, different serum panels, and some additional antigens for both influenza A and B viruses. What I can state in brief is that, although the amount of data was expanded

pretty dramatically, the additional serologic data were very similar to the data that had already been presented to the Committee in January.

Just to mention briefly, the data continued to indicate that current vaccines from whatever source containing the A/New Caledonia/20/99 component as the H1N1 strain and A/Panama/2007/99 as the H3N2 strain provided very good coverage for the circulating H1N1 and H3N2 subtype influenza A viruses. But very much like what we had seen here earlier, the data also demonstrated that there were moderate reductions in response to the circulating influenza B viruses, particularly those that were very definitely B/Sichuan/379/99-like; and of course, the current vaccine contains the B/Yamanashi/166/98 strain.

In terms of the strains and reagents, we have also been collecting a lot of additional information about them, and at this point there are quite a few candidate strains that the manufacturers are providing feedback to us about.

The additional influenza B viruses that have been distributed are not all in the same stage of being assessed, and there's still some discussion going on. Just as we had in January, there's still some mixed feedback from the manufacturers about how

they see these different strains.

There's very generally good agreement that the B/Johannesburg/5/99 strain is low yielding, and most manufacturers would prefer not to use that strain if they are going to achieve high enough yields for timely production. It's clear that it could be used for manufacturing if it was absolutely necessary, but it would mean that there would be a lot less vaccine that would be produced if that strain were used.

The B/Victoria/504 strain appears to be the best strain for growth when it's assessed based on the hemagglutin titer, but some manufacturers have expressed some reservations, because what they have seen, as with some of the other B/Sichuan-like strains, is that there's somewhat of a fluctuation from passage to passage for the B/Victoria/504/2000 strain.

They are concerned that this might lead to some unpredictability in the yields that they would get through the process, and so not all of the manufacturers are convinced that that would be the best strain.

The B/Guangdong/120/2000 strain is also being assessed. That was mentioned on one of the slides that Nancy showed a few minutes ago. From a

growth characteristic point of view, it seems to be almost as good as B/Victoria/504, although not all the manufacturers agree that that's true.

Some of the manufacturers are also reporting to us that they believe that this strain is more stable in its titer and, therefore, they would have a little bit more confidence in the performance of that strain from batch to batch as they would be in production.

Unfortunately, at this point the antigenic characterization of that strain has not been completely -- It's not been completed, and there's not total agreement as to whether this strain would truly be appropriate for manufacturing.

In terms of the reagents for manufacturing, the reagents for a New Caledonia/20/99(H1N1) and for the A/Panama/2007/99 strain, both the antigens and the antisera that are needed for potency testing are available now as needed, and there is no problem with access to those for manufacturers of an activated influenza virus vaccines.

Previously, there were some reagents made by the Therapeutic Goods Administration of Australia, and we talk about them as TGA. So if I forget and use

the acronym, that's who I'm talking about.

They have made reagents for both the B/Johannesburg/5/99 strain and the B/Victoria/504/2000 strain, and were supporting those vaccine components for vaccines being prepared for use now in Australia and other parts of the Southern Hemisphere. However, those reagents were in very limited supply, and they are no longer available either through the Center for Biologics or from TGA.

NIBSC in London has prepared an antigen and an antiserum for use with the B/Johannesburg/5/99 strain. Those reagents are also available from NIBSC. However, we are in the process of preparing reagents for use with B/Victoria/504/2000. Those reagents from us will not be available until May at the earliest. That's usually true when there's a strain change, and this would be typical for what would be expected for production of new reagents.

If there are some other strains that are chosen for use in inactivated vaccines and, in particular, any new B strain that would be chosen now that hasn't already been discussed, we would have to make some arrangements on tight schedules to try to prepare additional reagents for potency testing, and that would be -- could be somewhat of a rate limiting

step for the manufacturers in terms of doing their production for the year.

Of course, as an interim measure for any new strain that gets used, the manufacturers can use the old reagents to get an idea of where they are, although we know for certain that use of the old reagents will give a higher estimate of what the yield actually is, and they won't know until they have the specific reagents to know exactly what they are getting in terms of yield for production.

Therefore -- I'm not sure I'm paraphrasing this right, but an over-exuberant enthusiasm should be avoided in the absence of the specific reagents.

So if you would like me to go ahead -- If there are questions or comments from the Committee at this point?

ACTING CHAIRMAN DAUM: Are there questions at this time for what's been said so far? Dr. Griffin?

DR. GRIFFIN: I am just curious. It sounds like different manufacturers are getting somewhat different results with a couple of the candidate strains, and do they all have to use the same one?

DR. LEVANDOWSKI: Well, there are two

strains that are already being supported worldwide that are Sichuan-like, the B/Johannesburg/5/99 strain and the B/Victoria/504.

To answer the question directly, do they all have to use the same strain, no. We've had instances in the past when manufacturers -- some manufacturers have used different strains. It really becomes a matter of trying to make the reagents to support that and how we can get those, and the reagent sets are actually made.

The antigen that's used for production is actually a whole virus vaccine product that is made by a manufacturer. That's true everywhere in the world. So in order to do the test as it's been done at this point, we would need access to such a reagent, and we would have to find a way to produce that.

If the manufacturer that wanted to use a different strain -- If they wanted to do that, they would probably have to be able to supply us with the material to be able to do that production.

So we are willing to, and I think it's okay to support that. The other consideration here would be the confusion that is caused by all the different names of the strains that are out there. We talk about the recommendation from the WHO, for

example, as being an A/Moscow/10/99-like strain, but we all know that it's actually the A/Panama/2007/99 strain, and that does cause people to worry about am I getting last year's vaccine or am I getting the current vaccine.

So we have a consideration in that respect as well, although I think it's less important than the consideration about whether the vaccines can actually be made.

ACTING CHAIRMAN DAUM: I think we'll go on then.

DR. LEVANDOWSKI: Okay. Well, we'll go ahead with the options here. Just to review then, for what we've heard about the H3N2 viruses, there have been very few influenza A(H3N2) viruses that have been recovered this year.

The HA of most of these strains are antigenically very similar to the A/Moscow/10/99 strain and to the A/Panama/2007/99 strain, and these H3N2 viruses are generally very well inhibited by the antisera from people who have been immunized with the current vaccines containing A/Panama/2007/99.

In addition, high growth reassortants for A/Panama/2007/99 are available. They do grow well, and the manufacturing is now very well worked out. So

for the H3N2 strain, the first option, of course, would be to maintain the current vaccine strain.

In favor of that, as we had discussed before, the manufacturing is worked out. the yield is very predictable at this point. Most of the viruses this year are A/Panama/2007/99-like by their antigenic characterization, both for the hemagglutinin and also for the neuraminidase.

On the non-pro side, I really don't have anything to offer at this point for that option.

To go on, the other option is to change the current strain to something that is more representative of currently circulating viruses. At this point, really, the only alternative high growth strain that would be available would be this A/Ulan Ude/01/2000 strain which, as we had heard in January, has a neuraminidase that genetically is more closely related to the circulating strains. But as we also heard this morning, antigenically it does not appear to be divergent.

So for our purposes the antigenic characterization is more important and more relevant to the immunologic responses that people are going to experience when they get the vaccine.

So on the con side here, a new strain, of

course, may not be superior. It may not give any superior coverage to the current vaccine strain, and there are manufacturing issues that would need to be worked out that have not been addressed at this point for that particular strain.

So you just hold on for a second, and then going on to the influenza B viruses, what we've seen is that antigenic drift is continuing. Most of the strains are antigenically distinguishable from the current vaccine strain, which is B/Yamanashi/166/98.

A new variant that is represented by the B/Sichuan/379/99 reference strain has been identified, and it clearly is spreading widely. There is evidence that the strains that are related to B/Sichuan/379/99 are less well inhibited by the antisera from people who have been immunized with the current vaccines containing B/Yamanashi/166/98.

There are several vaccine candidate strains that are B/Sichuan-like that are being assessed, and it seems likely that one or more of these will be acceptable for large scale manufacturing.

The B/Sichuan strains such as B/Johannesburg/599 and B/Victoria/504/2000 have been used for manufacturing, and although the

B/Johannesburg is low and would probably not be acceptable, the other strains probably are going to be suited for the large scale manufacturing and antigenically acceptable as well.

So the options for B, if we can just go on: The first option would be to retain the current vaccine strain, which is B/Yamanashi/166/98. The only thing that I can find in favor of that is that manufacturing is very well defined, and it's very predictable. But against that, the new variant strains that are recently identified are clearly spreading, and they are increasing at proportion and, furthermore, not well inhibited by the current vaccines.

So the other option here at this point is to change the strain. Option 2 would be to change the strain to a B/Sichuan/379/99-like strain. In favor of that, of course, the vaccines might provide broader coverage for the current influenza B viruses. We can never tell that for sure until the vaccine is made and is in use.

Several candidate strains have been identified, and they are being examined against this. However, some of these strains that have been assessed are not going to be adequate for manufacturing and, of

course, the new strains, whatever they are, can always have some unpredictable difficulties that may not show up until manufacturing is really underway, as we have seen in past years. This would be nothing new in terms of experience in the past, but it's something that would need to be considered.

I guess I will stop there and turn this back to you, Dr. Daum.

ACTING CHAIRMAN DAUM: Thank you very much. Are there Committee questions regarding Dr. Levandowski's presentation of the options? Dr. Decker, please. Then Dr. Kohl.

DR. DECKER: Roland, would you recapitulate what --

ACTING CHAIRMAN DAUM: Could you speak into the microphone, Mike, or turn it on or something.

DR. DECKER: Would you recapitulate what considerations, if any, might favor Guangdong and what would disfavor that choice?

DR. LEVANDOWSKI: Well, what would favor it would be whether a manufacturer could use that strain. We would have to support that with reagents as well. So there would have to be some way to work out production of the reagents for potency testing to standardize the vaccine for hemagglutinin content.

DR. DECKER: These sound like the disadvantages. I thought you indicated that you thought there might be some advantage to Guangdong.

DR. LEVANDOWSKI: Well, what I indicated was that some -- Maybe I didn't state that clearly. But some of the manufacturers have indicated to us that they see Guangdong -- the Guangdong/120/2000 strain as having growth characteristics that are almost but not quite as good as the B/Victoria/504/2000 strain.

Some manufacturers have expressed the concern about the fact that, for the B/Victoria strain, some passages -- There's been some fluctuation in HA titer as the strain has been passaged. So they have a concern about how stable that strain would be and how it would behave in manufacturing.

There may be some further issues that specific manufacturers have about how things go through the process. Many manufacturers -- Actually, we may have some additional information from our colleagues in Europe.

Many of the manufacturers in Europe have capability for doing small scale processing and do so to try to assess these strains, and we actually do expect to get some feedback from manufacturers in

Europe in that regard, probably in the next week or so, related to the Guangdong strain itself.

DR. DECKER: So at this moment, although people aren't perfectly happy with Victoria, there is no reason to presume that Guangdong would end up being any better, and it would pose the problem of having to develop the reagents?

DR. LEVANDOWSKI: Yes. But as I also said, we have supported more than one strain in the past, and you know, we'll do our best to try and support that, if it's necessary. If this looks like the best option for some manufacturer, we certainly are not going to reject that idea that another strain may be -- as long as it's antigenically acceptable, may serve the purpose.

It certainly causes confusion to have multiple strains in use, but I guess we always are dealing with the issue of communication about influenza. It's a very complex situation always to try to communicate what is happening for all these different strains that have names that people don't really want to hear about, much less the simple things about how to administer the vaccine.

ACTING CHAIRMAN DAUM: Dr. Kohl?

DR. KOHL: Roland, thank you for a nice

presentation, as usual.

I'd like to broaden the scope a little bit to touch on our, as Dr. Katz said, fragile vaccine system at this point. Is the system anymore robust than it was last year, and given what you are describing as potential problems of reference material available to manufacturers, potential problems of growth of a new B isolate or new B antigen, are there contingency plans for making sure that this year vaccine gets to high risk people before it gets to supermarkets and shopping centers?

DR. LEVANDOWSKI: It's always a concern for FDA and CDC and the Public Health Service generally that the vaccines be made available. So, yes, we are doing the best we can to try to plan for whatever may come to us in terms of manufacturing issues.

We do the best we can, I think, to try to support the manufacturers by CDC, by finding -- and the World Health Organization generally by finding as many isolates as possible that might be appropriate for manufacturing.

I guess, to give some reassurance, I have heard -- I have heard some confidence expressed by some of the manufacturers for the B/Victoria/504

strain based on their experiences in the past with similar kinds of viruses. That's not to say that they won't run into difficulties early on in manufacturing, but the fact that they are saying that to me suggests to me that it's unlikely that they will run into something more than the typical problems that they have to deal with.

I don't think that there's going to be some major surprise. There may be some variability in the manufacturing. Yes, that's always true, but I think in general, maybe I should give reassurance that we don't anticipate that there would be some insurmountable problem at this point with supporting a B/Sichuan/379/99-like recommendation. We think we have the capability to deal with that.

ACTING CHAIRMAN DAUM: Thank you very much. Dr. Decker, then Dr. Kim.

DR. DECKER: I have some information that may help respond further to Steve's question.

The problem last year really had two roots. One was the production problem and the dropout of two manufacturers, basically, which was unprecedented, those things happening simultaneously. The other one was the demonstration that in that circumstance the distribution system didn't work well,

and steps have been taken to address both of those.

With respect to production, the company that produced the largest volume of vaccine last year expects to be able to produce substantially more this year, up to 55 million doses, which would actually cover any defect caused by another manufacturer unexpectedly dropping out.

So supply -- Assuming things work the way they are supposed to work, supply shouldn't be a problem. On the distribution side, that large volume manufacturer has taken steps to limit distribution so that nobody will get their full order initially. Rather, everybody will get half their order or part of their order to ensure that no one is left unable to immunize their high risk people.

Given the restrictions of our laws and society where you have to honor contracts, that's the best a manufacturer can do. But those two steps -- Either one of those steps should be enough to address last year's situation. The two taken together, it is hoped, provides some redundancy so that that won't arise again.

ACTING CHAIRMAN DAUM: Thank you. Dr. Kim, please.

DR. KIM: In looking into Nancy's handout,

page 11, Victoria/504 -- B/Victoria/504 has a -- in addition to recent Hong Kong isolates, also had a decrease activity against a strain named the 24, B/Shenzhen/877. This is a fourfold decrease.

Is there any information available whether these types of a B strain is prevalent or what's the magnitude of a Number 24-like strain in the influenza B?

DR. COX: No. We know that we have a proportion of viruses that are low to Sichuan. We were seeing this before. Oftentimes, they are low across the board. You have pointed out one of the examples where we are not -- with some new antisera we are not seeing it low across the board, but low with some specific antisera.

We are going to be doing more testing to see if this is consistent and so on, but we -- And of course, we will be putting some of these viruses into ferrets -- additional viruses into ferrets. We have already put some in, and very often what you see is that you get a low homologous titer, which often indicates that the virus is low avid.

So it's not a true antigenic variant. It's simply a virus that, for whatever reason, does not have a very high affinity for antibody. So we are

exploring these, but right now they don't fit into any category. It isn't a situation where we can identify a new variant that is emerging on top of the B/Sichuan-like viruses.

ACTING CHAIRMAN DAUM: Dr. Kohl, then Dr. Eickhoff.

DR. KOHL: Nancy, is the B/Shizuoka/480 a possible manufacturing antigen? It looks like it had really nice cross-reactivity in the tables you handed out.

DR. COX: The B/Shizuoka was distributed to the manufacturers, and I don't believe that they have had very good success with that particular strain. It was being explored in Japan. It was one of the strains that was explored, because the Japanese manufacturers, at least initially, indicated that they thought it was doing well. But that hasn't seemed to -- It hasn't been a consistent finding.

ACTING CHAIRMAN DAUM: Dr. Eickhoff, please, then Dr. Levandowski. Did you want to speak to this? Hold, Dr. Eickhoff, one minute, please.

DR. LEVANDOWSKI: Yes. I just wanted to add a little information. That's correct. There are probably, I think, about 15 B strains that have been distributed to manufacturers that are Sichuan-like or

something in the new category, and only three or four of them really have appeared to be high growth.

Shizuoka is not one of those that looked it grew very well for any manufacturer. Another strain that we really didn't talk about or concentrate on is the Perth/02/2000 strain. That one also seems to be -- would be maybe the third choice after Victoria and Guangdong.

So that's a consideration also, although it's not getting that much attention from manufacturers, but that seemed to be -- Those are the top three.

ACTING CHAIRMAN DAUM: Thank you. Thank you, Dr. Eickhoff, for being patient.

DR. EICKHOFF: Thank you. This is a two-part question addressed primarily to Roland, but I guess, to some extent, also to Mike Decker.

Given the current manufacturers and given that everything works more or less smoothly, what's the total manufacturing capacity for influenza vaccine in the United States? That's question one.

Question two --

ACTING CHAIRMAN DAUM: You turned your head at the key moment there, Dr. Eickhoff. Can you repeat the last part of that question.

DR. EICKHOFF: If everything works well, how much vaccine can U.S. manufacturers or can we make in the United States?

Question two: As we sit here this morning, am I correct in assuming that there have been no substantive changes to the distribution system in this country once vaccine leaves the shipping dock at the manufacturer?

ACTING CHAIRMAN DAUM: Thank you. Responses? Dr. Levandowski?

DR. LEVANDOWSKI: Okay. I'll speak to question one only, and actually others could probably speak to this, too.

It seems to me that at the ACIP meeting a few weeks ago, the manufacturers who were represented there indicated that they thought their total capacity for this year might be in the range of 80 million doses.

I believe that the representative from Aventis indicated that they thought they could produce 55 million doses. Someone from Wyeth indicated 25 million doses, and I think that the Medeva people were quoted as around 10 million.

So I believe that's what they have indicated they think their capabilities are, and

that's very much in line with what has been happening over the past five or six years.

ACTING CHAIRMAN DAUM: Thank you. Dr. Katz, please. Did you want to speak to this question, Michael?

DR. KATZ: I thought that he asked Mike Decker to say something.

ACTING CHAIRMAN DAUM: Well, he did. But I didn't know whether Michael wanted to.

DR. EICKHOFF: Well, Michael partly maybe can answer the question about distribution system.

ACTING CHAIRMAN DAUM: Excellent. I'm all for clarity. Go ahead, Dr. Decker, and then Dr. Katz.

DR. DECKER: Ted had a two-part question, and the second part, the distribution question, I already answered that in part in terms of how the large volume manufacturer is going to regulate their distribution to ensure that everybody gets part of their order.

Then it will be up to the recipients to ensure that they use that part to immunize the right people. The manufacturer can't do that for them, but they will get enough vaccine early to make sure they immunize their high risk people.

The second part of it: Part of the

problem last year was that so much of the production went based on existing signed contracts to distributors over whom no one had any control. That's why vaccine early in the system showed up in places that irritated people.

Our experience was that, as the message became better heard about the need to prioritize, there was a redistribution of vaccine, and the early season problems appeared to be correcting themselves late in the season.

Part of the message that we've mentioned at NVAC and ACIP that we thought we perceived out of this is that, although those of us in public health hear very well and very early the message, those who aren't attuned to reading the MMWR and aren't attending these meetings don't hear it very well at all, and we had a communication shortfall, and by "we," I mean the whole public health fraternity had a communication shortfall, and the distributors and the grocery stores weren't hearing this message until it got so loud that it spilled over well into the public press, and then they heard it.

So part of last year's problem was the unfamiliarity of the totality of the distribution chain with the need to prioritize, and they are now

sensitized to that.

So I think both the changes in the distribution rules and the attention from last year are going to help that problem.

ACTING CHAIRMAN DAUM: Thank you. Dr. Katz, then Dr. Faggett.

DR. KATZ: Well, I think Dr. Decker answered in part what I was going to say, in that the impression we were given was it isn't the manufacturer who sends it to the public health clinic or to the physician's office.

He sends it to a distributor, and it's the distributor then who has the option of where it goes and whether his annual contracts who buy a given number of doses every year get it first or Dr. So and So who takes care of geriatric patients gets more this year, because you're saying it's a shortage year.

I think it's important to realize two things happened. The delay was such that CDC ordered and bought an extra 9 million doses, and 7.5 million of those doses are still sitting there, because they were never used. So that sometimes the public perception and the actual utilization may be awry, and I don't know what NIP will do with its extra 7.5 million doses. I don't know if you will buy them

back, Michael, or not.

I think the other issue I wanted to ask Roland about was: We were told that one company had dropped out. Is that just for this year or is that company dropping out of influenza virus vaccine production, quote, "permanently"?

DR. DECKER: If you are referring to Parkdale --

DR. KATZ: Yes.

DR. DECKER: -- they had press releases indicating that they were permanently leaving production of influenza vaccine. That's my understanding from what I've seen in the press.

DR. KATZ: The other issue was several of the pediatricians who were interested -- there are some vaccines that are licensed for children down to six months of age. That other vaccine was only licensed for children four years of age and up.

So if you were going to get into childhood immunization, you were constrained not because anyone ever showed it was a bad vaccine in younger children, but it had never been tested in younger children.

ACTING CHAIRMAN DAUM: Okay. We are going to try and steer the conversation toward the issues focused on strain selection. Dr. Faggett and then Dr.

Decker, please.

DR. FAGGETT: Right. Just one comment. Dr. Eickhoff raised the question in terms of distribution, and Dr. Katz and I were privy to the Institute of Medicine review showing how the state infrastructure for distribution was really inadequate in some instances.

So it's going to be dependent on 307 funding and a lot of things like that as well. So I think that's another consideration. I don't know if, Dr. Decker, you have any information that is a state infrastructure now better capable of distributing?

DR. DECKER: Well, I'm not the one to answer that question, and I don't know if there is anybody here from CDC who really works at that, that's in a position to answer it. Nancy, can you handle that?

DR. COX: I really can't answer that question with the answer that you would like. It's actually going to take funding and time to build the infrastructure within the states to deliver influenza vaccine.

DR. FAGGETT: Yes. We recommended that they made more, so they should get that.

DR. COX: We are working extremely hard --

Walt Orenstein and his group are working extremely hard to try to increase the resources that are available for CDC to distribute to the states to try to improve this infracture for influenza vaccine delivery, and there is a general consensus among public health authorities that this would really help a great deal in the future.

ACTING CHAIRMAN DAUM: Thank you. Michael?

DR. DECKER: One last -- I know you want to get back on topic, Bob. But the drift of the Committee into this area is an evidence of the concern and interest, and I have one more piece of information that a couple of questions or comments suggested was still necessary to pass out.

Although this was discussed at NVAC and ACIP, don't underestimate the economic issues involved here. Parkdale is out, because there is not enough money to be made in the flu business to pay for bringing their factory up to standards, and they said that very clearly in their press release. This is the cheapest vaccine sold. It's basically sold at a commodity price.

The question was asked by Ted about how many doses were being made in the U.S. Let's remember

that one of the three manufacturers makes their vaccine in England, and they make vastly more in England than they sell in the U.S., because they can sell it for a lot more money in Europe.

We get their leftovers. We're the Third World country for influenza vaccine. We could have had plenty of vaccine to solve our shortage last year if we were willing to pay as much as Europeans pay for it.

ACTING CHAIRMAN DAUM: And why aren't we? Companies have never been shy about charging before, to my knowledge.

DR. DECKER: I can't answer that.

ACTING CHAIRMAN DAUM: Okay. Good. I think -- Thank you very much.

I think it would be good to go on at this point, having heard the options for strain selection, to the open public hearing portion of this morning's session, and at this time ask individuals in the audience who wish to speak to come forward and be heard.

I think we have had an appropriate hiatus, and what I'd like to do is to move into the Committee discussion and voting and finish this item, then break, and then we'll consider the issues related to

Session 9.

So, Dr. Levandowski, let me ask you to provide one more piece of orientation for us. When we met last in January, I thought this Committee did quite well, frankly, in terms of providing guidance as to our thoughts about what should be in next year's vaccine.

We were a little vague about which B Sichuan-like strain to replace the current B Yamanashi-like strain on purpose, because of the issues that you raised, and others, about growth and manufacturing and reagents and left latitude.

We were fairly specific about the type A issues, although we are always anxious to have more data. I'm struck by the fact that the neuraminidase concern that we had in January -- more data does not appear to have more concern associated with it.

I am also struck by the analysis of further Type A viruses that appear to be similar to the data that we heard in January, no new directions or major concerns there; and I am again struck by the fact that our B analysis in January appears to have been on the money and that the notion that a change was in the cards was a good decision.

What would you like us to accomplish this

morning? We can rubber stamp and say we've heard the new information, and we affirm what we said in January or we can try and be more specific for you.

DR. LEVANDOWSKI: Okay. Well, I guess our intent -- As you know, I mean, these meetings have to be scheduled long in advance of the time that they actually occur. So that some of what we are doing today we couldn't anticipate whether there would be changes that would occur in between January and March, and as you know, the January meeting has been established to try to give manufacturers some information so that they can begin what is a very long and arduous task of making vaccine.

It is important for them to have some notion of what direction to be heading, but again we don't always know that things are going to work out so clearly. I guess I would comment that this particular year has been a little bit different from what we have experienced in many of the past years, partly because everything does seem to be more -- or seems to be a lot clearer in terms of what the epidemiology and surveillance is, and also just the overall nature of what's been happening with influenza has been so quiet that there is not as much to talk about as we sometimes have.

So I guess, if you would be comfortable in affirming your recommendations previously, I think we would be -- we and the manufacturers would be completely understanding of what you tried to tell us before and what you are telling us here again this morning.

If there's a concern about the B strains not having -- at this point having a very specific notion of which of the strains to be used, I guess I would ask the Committee, as has been done in past years -- it would not be a precedent -- to permit those of us in the Public Health Service and the manufacturers to work out what the actual B/Sichuan/379/99-like strain might be, if that's what the recommendation is.

ACTING CHAIRMAN DAUM: Very good. So here's some guidance for discussion. Maybe there won't be a lot of discussion. We'll see.

We've heard new information. We thank our colleagues very much for the update, but it looks like we were pretty good in January, to me. What I'd like to hear is if people disagree with that assessment and want to put different ideas on the table.

Do we need to have a motion and a vote? Let me get this clarified first, Michael, please, or

are we comfortable without that? FDA people?

MS. MIDTHUNE: We can just go around and say agree, agree, agree or not agree.

ACTING CHAIRMAN DAUM: Fine. Okay, let's hear from -- Thank you, Dr. Midthune. Dr. Decker, please.

DR. DECKER: I agree with the thrust of what Roland said. My only suggestion would be -- really, subject to Roland's comment, would be that perhaps we ought to make more clear recommendation at this time for B/Victoria with the understanding that, should a clearly superior strain be identified, there is the option to switch. But where we left it last time, we didn't clarify between Johannesburg and Victoria, and the data available now seem to suggest that the Victoria is a better strain.

I think there is a public health benefit, all else being equal, in the manufacturers having a common choice. so to the extent we can provide a little bit sharper guidance today on that, we may achieve something with some public health benefit.

ACTING CHAIRMAN DAUM: And yet the downside would be that we would tie somebody's hands.

DR. DECKER: No, I'm not trying to tie hands. What I'm saying is that we could make it a

little less vague than we had it in January. It's just a slight difference, but in January we were considering Johannesburg and Victoria in equal play, and the data now suggest that Johannesburg is not a good choice.

Victoria is the best known present choice, but we would still allow Roland and the manufacturers to agree on a third alternative, such as Guangdong, if it turns out that there is really superior.

So we are sharpening it a little bit, removing a little bit of the imprecision.

ACTING CHAIRMAN DAUM: Dr. Levandowski, could you be heard on this issue, please?

DR. LEVANDOWSKI: I think that it would be possibly in the interest of people using these vaccines that you not be too specific about what the strain ought to be. Now what I'm thinking about is if, say, there are travelers who go to another country and they want to use a vaccine that's in use in Europe, and it says B/Johannesburg/599, for example, that they know that we think that particular strain is okay.

I think what we don't want is to eliminate the possibility that somebody could manufacture and that there could be use of another influenza B virus.

We don't really want to have confusion. It is better in some sense to have a limited number of options and to stick with what seems to be the best option overall, but again there will be vaccines elsewhere in the world that will not necessarily be B/Victoria/504.

I do think we want to be sure that we are not sending a message to anybody that we think that those strains would not be acceptable for use.

ACTING CHAIRMAN DAUM: I'm hearing from that that we should stick with what we said in January. But let's get Committee input on that, and we can certainly have -- agree or disagree as we go around, but let's hear from everyone. Steve, would you start, please?

DR. KOHL: I'd like to affirm our recommendations that we made in January, that the H3N2 strain for the coming year be the A/Panama/2007/99, and that the B strain be a B/Sichuan/379/99-like strain such as B/Vic/504 or B/Johannesburg/5/99 or another suitable strain that comes up.

ACTING CHAIRMAN DAUM: Dr. Kim, can we hear from you?

DR. KIM: Yes. I'd like to continue to support the recommendation being made by this Committee last January for the selection of influenza

A and B viruses.

ACTING CHAIRMAN DAUM: Thank you. Dr. Faggett.

DR. FAGGETT: I agree with the previous speakers.

ACTING CHAIRMAN DAUM: Thank you.

DR. GRIFFIN; I agree.

DR. DIAZ: Likewise, I agree.

DR. KATZ: I agree.

DR. GOLDBERG: I agree.

DR. EICKHOFF: I agree.

ACTING CHAIRMAN DAUM: Dr. Butler? Agree?

DR. BUTLER: Agree.

DR. HALL: Agree.

ACTING CHAIRMAN DAUM: You are now a speaking member. Ms. Fisher is not here. Is that correct?

MS. CHERRY: No, she's not.

ACTING CHAIRMAN DAUM: She's not? Okay. Would you like to speak to this issue or not?

MS. LIBERA: Only a couple of comments. There seems to be a lot of mixed signals concerning flu shots to the public. Every year there is a -- you know, the age ranges, whether you really can get the flu from the flu shot itself. We spend an awful lot

of time convincing people, even healthy people, to get flu shots.

So I would hope that there would be -- I guess I'm a little confused about the manufacturers saying that they can supply it without knowing exactly what it's going to be. Also, I don't remember in the past manufacturing problems, and I don't -- either I just wasn't aware of it or it just got more publicity this year. So I'm curious about why that happened.

I guess that's all I have to say.

ACTING CHAIRMAN DAUM: Okay. I'm going to sort of note those comments, but we had had the discussion period, and I think we are now at the point of deciding whether we agree or disagree with the January recommendations. So with your permission, I will note those questions, and I'd like to at least get finished getting a consensus here.

I guess we are finished except for me, who agrees. So I think you have your answer from the Committee.

Is there anyone else who would like to say anything about influenza? Dr. Decker, of course.

DR. DECKER: Just a question, and clarify it for me, procedure. Based on what was just done, are the manufacturers now free to go into production

with one of the strains that would be consonant with this recommendation or are there still discussion steps with FDA and CDC that have to occur and some agreement among you, Roland, and your colleagues and the manufacturers on what the actual strain would be. How does that work?

ACTING CHAIRMAN DAUM: Dr. Decker, I'm not sure we need to hear this discussion. The Committee's task is to give advice to the FDA about strain selection, and what happens between the FDA and the manufacturers, I think, goes beyond the scope of what we're doing here.

DR. DECKER: Well, I don't think it's completely irrelevant, because we had the problem last year because three things happened in confluence. There was a late recommendation leading to late initiation of production. There was a delay -- There was a production problem, and then manufacturers fell out.

So what I'm actually asking is have we now solved the late recommendation issue or have we -- are we still, in fact, absent a firm, reliable recommendation on which production can start? So it goes to the heart of what we were talking about earlier.

ACTING CHAIRMAN DAUM: Dr. Levandowski, would you like to respond to that? You are welcome to say no.

DR. LEVANDOWSKI: Well, I'm trying not to say no. I think that the information from the Committee and the information that we have provided suggests that the B/Victoria/504/99 strain will be acceptable. It's already been used for manufacturing worldwide. I don't see any reason that we would want to reject that, manufacturers who want to use that strain, or if they want to use the B/Johannesburg/599 strain, I think we are prepared to try to support that.

When I say that, if you are going to ask me the next question, are we going to make reagents in the United States for B/Johannesburg/5/99, the answer is no. We will share reagents with our colleagues at NIBSC, as we have done in similar situations in the past where there's been more than one actual strain that's been used for manufacturing.

We will be making reagents to support the B/Victoria/504/2000 strain for manufacturing and, as I mentioned, if there are other strains that are necessary, we are going to find a way to support those also. But for that, we need help from the

manufacturers.

So I think our answer is that, both in terms of the B/Johannesburg/599 an the B/Victoria/504, which are already widely in use and are being supported and will be supported, there's not really any question about the validity of those strains for use in manufacturing. It's other strains that we would have to assess at this point.

So I guess that is the answer to what you are concerned about, what the manufacturers will understand from this session.

DR. DECKER: Good answer.

ACTING CHAIRMAN DAUM: Thank you very much. That brings this discussion and voting to an end. We will now take a break, a slightly long break. We can't really start the next session early, because we have people joining us by speakerphone.

MS. CHERRY: We can go into the open session.

ACTING CHAIRMAN DAUM: Right. But if we get done too early, we'll have to take another break. So I'd like to start at ten o'clock. So we will take a 20 minute break and resume.

DR. GRIFFIN: Can't you do the open session before so that we don't have to --

ACTING CHAIRMAN DAUM: I'm sorry. I don't completely understand.

MS. CHERRY: Well, we can go ahead. What he's saying: If we start the open session that is now scheduled for ten o'clock anyway, so if we take coffee break, that brings us right on time. We can't start the closed session until eleven.

ACTING CHAIRMAN DAUM: So we're taking a 20 minute break instead of a 15 minute break.

(Whereupon, the foregoing matter went off the record at 9:43 a.m. and went back on the record at 10:10 a.m.)

ACTING CHAIRMAN DAUM: Good morning, and welcome to Session 9, the briefing on activities in the Laboratories of Retrovirus Research and Immunoregulation.

I'd like to go straight into our business here and call on Peter Patriarca to introduce the laboratories and the review process.

DR. PATRIARCA: Thank you, Bob. If somebody could turn on the slides.

ACTING CHAIRMAN DAUM: He says he's ready to go, Peter.

DR. PATRIARCA: Okay. Can everyone hear me okay? I'd just like to briefly introduce the

session by giving the Committee a little bit of background about the Division of Viral Products and also to remind them of the important role that they have in helping us make management decisions and resource decisions about the workings of our research programs.

I'd just like to remind the Committee that the Office of Vaccines Research and Review headed by Dr. Karen Midthune has three divisions. There are two laboratory based divisions, one the Division of Bacterial, Parasitic and Allergenic Products that is headed by Dick Walker, and then Division of Viral Products headed by myself.

There is also the Applications Division, which is composed of desk based scientists as opposed to laboratory based scientists, headed by Dr. Goldenthal.

Within the Division of Viral Products we are organized into eight different sections, seven of the laboratories and then also the Office of the Director. I think it's important to point out, particularly since the laboratory review today will focus on Dr. Golding and Dr. Berkower's lab, that the FDA and CBER specifically is unique among Federal agencies in the sense that HIV research and HIV

review, including HIV vaccines, is actually confined within the same division as other viral pathogens.

Very briefly, our mission and functions, as you might imagine, primarily encompass research and review. You will be hearing about the research programs today, and I'll mention a few things about the review situation.

I would also like to point out that we are also very much involved post-licensure surveillance. We work very closely with the compliance folks. We also focus in on adverse event review in collaboration with our colleagues who are responsible for the VAERS system.

We have a very active lot release testing and protocol review system. We are also very closely involved in labeling changes and promotional activities, and we spend a great deal of time in consultation with organizations on the outside, both governmental and non-governmental organizations, but in particular the manufacturers.

Now as you might imagine, looking simply at the names of our laboratories, you might imagine that we have very specific pathogen related priorities. But what may not be apparent are all the programmatic areas that we are particularly interested

in that involve collaborations across laboratories and areas of interest that are directly pertinent to the evaluation of vaccines.

I don't have time to go into these, but some of these you will hear about in more detail in a few minutes.

So I'd like to say that our laboratories are actually improperly named. For example, the two laboratories that you are going to hear about should be named something like this to reflect all the things that they currently do.

Let's talk a moment about our review workload. This shows what's happened since FY '94, continuing through last year. You can see from here that we have in essence over 4,000 pieces of paper that just come through just this division.

You can see that these are a variety of activities, and you will notice also the enormous workload we have in terms of INDs. Now I would mention that, in addition to the increasing workload, I would also point out that the complexity of these reviews is dramatically increasing as the vaccine era really goes more from traditional approaches to approaches that are discussed in some of Michael Crichton's novels.

So there are some really sort of science fiction approaches that are on the near term horizon which make our job much more difficult.

Now I would also like to point out a little bit about resources. There is good news and bad news here. The good news is that at least the number of people within the Division has not substantially changed over the last five years.

Just for your information, we have about 65 full time employees in the Division, and these are supplemented by about 40 contract employees, usually post-doctoral folks, who participate with the senior investigators in carrying out some of the research programs.

While the number of personnel has remained relatively stable, as you can see here, our internal budget has declined dramatically between FY '95 and '99, reduced by approximately 60 percent, six-zero percent. Now that's the bad news.

The other part of the good news is that, because of the extremely high quality of science that is done by many of the investigators in the Division, we've been very successful in attracting outside money. This comes not only from NIH, for example, from targeted AIDS grants, but also the National

Vaccine Program Office. It comes from the Department of Defense and miscellaneous other grant mechanisms.

Just to point out that in FY 2000, last year, this discrepancy has now really become enormous, so that only about 15 percent of our entire operating budget now comes from internal sources.

So what this means and the importance of the Committee's involvement in this is that we have fewer and fewer resources to do more and more things and that these external resources, while large, are devoted to very specific programs, leaving other core programs pretty much under-supported.

So this puts folks like me and the people higher than me in a position of making very difficult decisions about resource management, allocation to different research programs. So this is why your input is so important today, and the rest of the presentations then will delve into some of the specifics faced by Dr. Golding and Dr. Berkower who, as you will hear, are primarily involved in HIV related research.

If there are no questions, perhaps we could just proceed to their presentations.

ACTING CHAIRMAN DAUM: Are there Committee questions or things you want to ask Dr. Patriarca?

Dr. Katz, Dr. Kim.

DR. KATZ; Does the diminution of intramural funds represent something across the board in FDA or something that is targeted at your group?

DR. PATRIARCA: Generally speaking, what's happened over the years is that the agency's budget has been, quote/unquote, "flatlined." That doesn't sound so bad, except that what has happened is that the things like salary increases and so on have not been accounted for in this so called flatlined budget.

By the time it gets down to the Division level, the lowly division that actually does the work, a lot of things happen with that money. There are other important agency priorities, Center priorities. So that by the time it actually filters down to the Division -- now granted, some of the programs, obviously, that the agency has funded are extraordinarily important, and decisions have to be made about the relative importance of, for example, viral vaccines versus other things.

So the flow of money, I think, is very complex to explain and really differs from year to year.

ACTING CHAIRMAN DAUM: Dr. Kim.

DR. KIM: Knowing that about 85 percent of

your operating budget are derived from extramural funds, I think that certainly indicates the system may be very fragile and that whether you guys -- I am sure, looking to continuously some alternative resources. Can you share with us what, you know, those alternative resources might be in case there are some decrease in extramural funding in certain areas?

DR. PATRIARCA: That is a very difficult thing for us to do. Part of my job is basically almost like a fundraiser, an advocate, for the Division, trying to make people aware of -- as I think you've very accurately described -- the fragility of the research program.

We also are having difficulty in attracting new people, because of the resource problem. We are also getting to be a very top heavy organization in terms of most of the staff that are now -- For example, the laboratory chiefs are, by and large, eligible for retirement.

So even though things are -- we're trying to cope with this situation as much as we can, we're very worried about the future, and it is fragile. Any marked reduction in the availability of funds to us will, I think, severely compromise what we can do in the laboratory at least.

Of course, the review activities will continue onward, but part of that is attracting good people, good reviewers, good scientists. They are all very closely tied together. So you really have to have all of those elements in the system in order to have a well functioning review program.

ACTING CHAIRMAN DAUM: Dr. Diaz, then Dr. Kohl.

DR. DIAZ: It is my understanding -- and correct me if I'm wrong -- that despite having a huge role in some of the laboratory aspects of preparing for things like bioterrorism, the FDA hasn't really actualized a lot of the money that has been set aside for not necessarily specifically laboratory issues but that in general.

Do you anticipate seeing any of that in the future and, if so, how would that help your intramural funding in terms of those bars?

DR. PATRIARCA: Yes. Dr. Egan, Bill Egan, has just -- would like to address that.

DR. EGAN: I wold like to make just a brief comment about the funding. Peter has remarked about some of the intramural funding that has -- the internal funding and how that has been decreasing and the reason for it.

ACTING CHAIRMAN DAUM: We need some microphone support of some sort here. Otherwise, we are going to miss your pearls, Bill.

DR. EGAN: Dr. Patriarca has remarked about the internal funding and how that has gone down and some of the reasons for that, the flatlining of FDA's budget. But I'd like to make a little bit of comment about the external funding for FY 2000, you know, where some of that money came from.

It's external in one sense, and it's not external in another sense. For example, you know, over $2 million of that was from the Department for support of bioterrorism research. Another part of that money was Departmental money for pandemic influenzas. Part of that money was from the Department and from the NIH for vaccine safety related issues.

Now granted, this is one-time money, and it's hard to carry on programs in that fashion. It's internal and it's external at the same time, but it was in support of Departmental programs, laboratory based programs.

What will happen this year, we are still not completely sure. I just wanted to make a little comment about the kind of funding.

ACTING CHAIRMAN DAUM: Thank you. Pam, a follow-up question?

DR. DIAZ: That's the difficulty, as you are pointing out. It's sort of internal, yet external in that it's targeted for a specific issue, and yet how would you -- Would you mark that in these graphs as external or internal? Just out of curiosity, how do you see it?

DR. EGAN: Yes. A good portion -- I mean some of it -- for example, like for the National Vaccine Program Office. That's competed monies for special -- for investigator initiative -- well, no, mission related programs, and the same with some of the DOE money.

The bioterrorism money, the pandemic influenza money, a lot of the vaccine safety money, those were sort of Departmental targeted dollars toward laboratory programs within the Office.

DR. DIAZ: Right. Thanks.

DR. EGAN: But how we sustain them is going to be an issue, too.

ACTING CHAIRMAN DAUM: Thank you. Dr. Kohl, then Dr. Faggett.

DR. KOHL: I was impressed with the slide you showed of what you called pieces of paper going

across the Department or Division. I think it may not be obvious from what you said, but it's probably painfully obvious to all of us sitting here that the time, effort, anxiety, etcetera, in generating these external funds, the grants that have to be written, all the extra activity is anther piece of work that is an increasing burden to your position, and I think that is worth noting.

DR. PATRIARCA: Agreed. Thank you for pointing that out.

ACTING CHAIRMAN DAUM: Dr. Faggett.

DR. FAGGETT: Mine is a related question. with the criticality of your mission, it would appear that you really need permanent staff. I'm concerned that, rather than have FTEs, you have visiting fellows. You have to beg, borrow or steal staff to really get your mission done.

As Dr. Diaz has mentioned, your missions are multiple. Is there any relief in terms of getting more permanent FTEs for you to properly do your mission?

DR. PATRIARCA: It's a very difficult thing, because you've only really heard about the microcosm of my Division and, when you consider all the other activities that are going on throughout the

Center, including such important areas as gene therapy, for example, then there are important research -- or resource decisions that are made at the Center level and even the agency level to determine that.

The short answer, I think, to your question is that I think everyone recognizes the importance of what the vaccine related research divisions are doing. We certainly have advocates all the way up and down the line. People are aware of what's happening, but whether that will actually translate into more resources really remains to be seen.

ACTING CHAIRMAN DAUM: Thank you. One of the reasons that I was -- I must say, I was willing to serve in this capacity as Chair of this committee is to try and get some sense of helping with this problem, which I consider to be enormous.

The agency needs to be strong and vibrant and, if I might say editorially, conduct research and be seen in the academic and intellectual communities that they work in. Otherwise, it just becomes a regulatory agency that doesn't have real insight into the problems that they are working on.

If there are Committee members that are

interested in beginning to have discussions with me about how to best strategize and do this, I would like to hear from you after the meeting, and we'll get together.

I think now we need to move on. Thank you very much, and we'll call on Dr. Golding next, if she would, to tell us about activities in the Laboratory of Retrovirus Research. Thank you, Peter, very much for sharing your thoughts with us.

Dr. Huang, good morning. This is Bob Daum.

DR. HUANG: Good morning, everybody.

ACTING CHAIRMAN DAUM: This is Bob Daum speaking. I'm delighted you are here. I keep remembering to make some comments to this box sitting on the table, but now I've done it. We cannot hear you. We'll work on trying to hear you in the next little bit. We'll get the microphone lined up better or something.

The noise in this room, you should know, the background noise is awful.

DR. HUANG: Yes.

ACTING CHAIRMAN DAUM: You remember. We have a very loud heating system. We are also getting construction noises, and we'll check in with you in a

few minutes and see if your hearing is any better.

DR. HUANG: All right. Thank you.

ACTING CHAIRMAN DAUM: We'll try to ask the microphone people to rev up the speaker so that you can hear better. Thank you very much, and welcome. We wish you were here.

DR. HUANG: I'm here.

ACTING CHAIRMAN DAUM: Okay. I mean here here, you know. Please.

DR. GOLDING: Thank you very much. I would like to really say that this is a real privilege for me to stand here and to present to you the program of the Laboratory of Retrovirus Research. It's a privilege and an honor, because I am lucky enough to head a fantastic team of not just highly qualified people, but really dedicated people to public health, and more than once during the past four years they were willing to put aside everything else that they did and respond very quickly to public health issues that helped to keep very important child vaccination in place. I hope some of it will be at least cast and shown in my slides.

So the Laboratory of Retrovirus Research is actually divided into three sections. I am also the head of the Section on Retroviral Pathogenesis,

and another independent investigator is Dr. Keith Peden who has been tenured in the past two years ago.

The other section is of Retroviral Immunology. It is headed by Dr. Dennis Klinman, and the Section of Molecular Retrovirology that is headed by Dr. Arifa Khan. Next slide.

So in order to set the ground for the scientific program, I think it's really important for you to realize the type of regulatory work that is covered by this laboratory.

The main -- One of the main areas, of course, is review of HIV vaccine applications. Both prophylactic and therapeutic vaccines get reviewed by members of our committee -- of our lab, and there are many types of vaccines that have been developed, starting from live attenuated vaccines to inactivated vaccine, peptide and subunit vaccines, live viral and bacterial vectors, nucleic acid vaccines and new adjuvant and carriers.

As you can see from the recent table that has been published in Science this month, the number of clinical trials that are either started, ongoing or scheduled to start in either 2001 or 2002 is quite large. I think there is a really big hope for the future of HIV vaccines, not just for this country but

globally.

If we look just to the type of vaccines that are going to be put forward and move into various phases of clinical trials, we have this very simple subunit vaccines to combinations of vectors and DNA, and bacterial lipopeptides, a variety of vaccinia vectors, and so forth.

If you think about the complexity of these vaccines, you start to realize how much expertise are needed to be evaluate them, both in terms of the manufacturing as well as the potential safety consideration, and very often the type of cell substrate that need to be used to produce these vaccines.

Another very important is we have been -- Our team has been reviewing plasmid DNA vaccines against viruses other than HIV and, as I mentioned to you just a minute ago, review of cell substrate used for viral vaccines and other biological products; because other biological products are also made in mammalian cells, monoclonal antibodies, gene therapies, and xenotransplants also pose unique issues, safety issues related to adventitious agents.

It's very important to have in the Center very sensitive assay for detection of known and

unknown retroviral contaminations and come up with a mechanism for removal or inactivation of retroviral contaminations.

We have also been assisting the Office of Therapeutics in review of some other anti-HIV and AIDS therapies, such as soluble CD4 and its derivative, some monoclonal antibodies, Kaposis sarcoma therapies, and our members have been participating in license applications, related viral vaccines and monoclonal antibodies.

So just to give you -- We all like to have a few numbers. If we just looked at the total submission of the LRR during the past three years, it went, the total submission from 270 to 310 in year 2000, and importantly, I think, is the number of original submission. You can see this recent boost in the number of original submissions.

I think it's great. It's really hopeful. It means that the sponsor out there, the industry out there, academia, international health initiatives believe that there is hope for HIV vaccines, and we want to work with them to see most and more of these vaccines getting into clinical trial, both in the United States and elsewhere.

So what is the scientific program that

needs to be in place to support this kind of regulatory challenges? So the overall goals of the lab is, first of all, to establish and develop new state of the art in neurological and virological assays to assure the safety and immunogenicity of candidate HIV and plasmid DNA vaccines, and to improve detection of retroviral contamination in cell substrates, vaccines and other biological products.

We also aim to conduct high standard research on HIV with emphasis on cell entry and viral tropism, animal models for assessment of HIV infection, candidate vaccine and biological therapies, new concepts in vaccine development, and viral genes and their role in pathogenesis.

I would now like briefly to describe to you the main PIs in the Laboratory of Retrovirus Research and outline their main scientific project and then, hopefully, to tell you at the end how some of this scientific work led to very important regulatory achievements.

So Dr. Dennis Klinman: As I mentioned, he is the head of the Section of Retroviral Immunology. He joined CBER in 1989 after five years as a medical officer and a senior staff fellow at the NIH. He brought a very strong background in rheumatology,

immunology, autoimmune diseases and in murine models of retrovirus induced immune abnormalities.

He established a highly productive research program on immune responses and safety of new vaccine candidates with emphasis in the past several years on DNA vaccine and CpG-containing oligonucleotides.

Just for a simplified version of a plasmid DNA vaccine, basically, as you know, all of these vaccines have some sort of antibiotic resistance selection marker that allows for large scale production in bacterial. In addition to the plasmid backbone, it expresses foreign gene. Here we show an HIV envelope. It can be multiple genes from different types of viruses, under the strong eukaryotic promoter. One of the most popular ones is the CMV immediate early promoter.

Dr. Klinman has spent a lot of time understanding these plasmids, how they work, and also identifying those motifs which are -- seems to be much more common in bacterial DNA and plasmid DNA compared to mammalian DNA, and they are highly unmethylated. These motifs, what's called unmethylated CpG, were shown to have very important adjuvant activity.

So as part of his both scientific and

regulatory work, Dr. Klinman studied the mechanism of action of DNA plasmid vaccines and potential of these novel agents to induce adverse events, autoimmunity and tolerance. Also the immune activation by DNA vaccine was linked to the presence of unmethylated CpG motif of bacterial origin in the plasmid backbone, and this motif may act as an immune adjuvant and function by inducing strong innate immune responses.

Dr. Klinman went on to show that this innate immunity can provide a very powerful antiviral and some even antibacterial responses that can precede the specific pathogen vaccination.

So the overall program in the past seven years in Dr. Klinman's lab, as I said, concentrated in various areas: First of all, immunogenicity of DNA vaccine, evaluate DNA vaccine in terms -- in Malaya, and HIV in three different species, mice, money and there are now human trials with some of these vaccines.

That was done in collaboration with investigators outside of the NIH -- of the FDA -- at the Navy; development of a DNA vaccine to anthrax toxin, which is part of the anti-bioterrorism effort; evaluated the activity and safety of cytokine-encoding plasmids such as IL-4, IL-12, Interferon gamma, GM-

CSF. This is a very important study, because several sponsors want now to add these kind of plasmid -- cytokine expressing plasmids to their antigen specific plasmid.

Studies the use of plasmid for gene therapy and the potential outcome, and he tested erythropoietin plasmid as a model.

Dr. Klinman also established the immuno-stimulatory activity of CpG, ODN in vitro and in vivo. He studied B cells, macrophages, dendritic cells and NK cells in a variety of species, mice, rats, rabbit, chickens, cows, monkeys and men. It does seem that this particular element seems to be very cross-species activities, although the sequences that are optimal for activation of the innate system in various species may vary.

He evaluated the therapeutic potential as vaccine agent, anti-allergens, immunoprotective agents, and monitored the intracellular pathway by which they induce cytokine production with emphasis on IL-12 and IL-6, also looked for ways to improve their uptake and activity using liposomes.

I would like now to shift to Dr. Arifa Khan. As I mentioned, she is the head of the Section of Molecular Retrovirology. She joined CBER in 1991

after ten years in the Laboratory of Molecular Microbiology at the NIH with Malcolm Martin.

She brought very strong expertise in retrovirology with avian, murine, feline, primates and human retroviruses. She established a scientific program that was aimed at development of monkey models for HIV infection and testing of new vaccines and therapies in such models; development and standardization of sensitive assays for the detection of retroviruses in cell substrates used for biological products.

In the area of vaccine safety, Dr. Khan conducted infectivity studies using a variety of human cell lines, indicated the absence of infection, integration and replication of retroviral particles that are present in all chicken cell derived vaccines. I'll get back to that aspect a little bit later, but that was part of the work that allowed us to alleviate the concern about measles, mumps and other vaccines that are made with chicken cells.

She was also providing important consultania in work on xenotransplant in primate cell derived vaccines by conducting analysis of naturally occurring simian foamy viruses for macaques, and she predicted reduced replication efficiency of primary

virus that are involved in cross-species infections to human. This is again very important aspect of how the research in the lab can add to the reduced -- to the evaluation of risks associated with renal transplant and the use of primate cells for production of biological product.

Her work also helps the gene therapy field, because she was able to show in vivo that murine replication competent retroviruses that occasionally contaminate gene therapy products may actually establish an infection and long term virus persistence in non-immuno suppressed rhesus macaques. That again may be a long term safety concern with some of the gene therapy products.

In another direction, she is involved in development of sensitive assays and strategies for detection of occult and adventitious retroviruses in vaccine cell substrates in biological products. Dr. Khan was the first to show that Mus dunni was identified as the most sensitive cell line for detection of simian foamy virus in primate cell substrate.

She was using PCR integration assays for detection of human infection with avian retrovirus sequences that are present in all chicken cell derived

vaccines. A quantitative real time TM-PERT assay was modified as a single tube assay with greater reproducibility and reduced background for detection of low level retrovirus particles, and chemical and biological agents are under investigation for activation of endogenous retroviruses in cell substrate.

Again, all of these studies are highly relevant to the regulatory issues that we have to face.

On the side of the HIV vaccine development, she has a long term interest in the development of the pig-tailed macaque with a preclinical model for HIV vaccine and therapeutics.

Dr. Khan was able to show transient replication and long term persistence of HIV in pig-tailed macaque. HIV multigenic DNA vaccines have recently been shown to elicit long term and boostable Gag and Env-specific humoral responses in these pig-tailed macaques.

HIV DNA vaccinated pig-tailed macaques boosted with gp160 were partially protected against challenge with HIV, and other HIV type viruses will be investigated for infection in pig-tailed macaques to develop the species as a model to evaluate the potency

and efficacy of HIV antiviral agents.

You are all aware of the fact that there are very few very good animal models for HIV vaccines. Most of the animals that are currently used have to use some form of SIV or SIV/HIV chimeric. The ability to identify new models that can be infected with HIV besides chimes, which are very expensive, will be very helpful.

Keith Peden, who is in the Section of Retroviral Pathogenesis, joined CBER a little bit later, in 1994, after seven years in Johns Hopkins University, a year at the Pasteur Institute, and five years as an expert visiting scientist in the Laboratory of Molecular Microbiology at the NIH.

He brought strong expertise in both DMH humoviruses, viral mediated oncogenesis, as well as lentiviruses, HIV-1, HIV-2 and SIV. He established a scientific program focusing on HIV/SIV accessory genes, HIV/SIV cell tropism, an adaptation to different target cells, and development of sensitive assays for detection of adventitious agents.

So the regulatory related research was -- Dr. Peden was really instrumental in the development of several quantitative assays to detect adventitious agents: First of all, retroviruses. He helped to

develop the PCR-based RT assays or the TM-PERT, which is at least a million times more sensitive than the previously used RT assays.

For DNA viruses, he has also developed a PCR-based assay to detect primate polyomaviruses using the TaqMan PCR technology, and looked at SV40, BKV and JVC. As you know, there was sort of recent suggestion that in some human tumors there are sequences of SV40. So as an agency, we have to address this issue, and it's important to develop highly specific assays to distinguish between SF40 and other human related viruses.

He is currently involved in a very important and exciting study on the formation of pseudotype between retrovirus core and the envelope glycoproteins from viruses of the paramyxoviridae and orthomyxoviridae.

It has a very kind of interesting potential safety risk evaluation, because it addressed the issue of what happened when we are infected with more than one virus at the same time. If we are infected with, let's say, HIV and measles, is it possible that some of the HIV can be coated with measle envelope and expand the target cells?

So these kind of experiments are both

cutting edge technology and allows us to evaluate all the potential risks associated both in terms of a disease but also in terms of certain vaccines.

Development of neutralization assays for viruses that did not replicate in vitro will greatly benefit from this pseudotype technology, and he already was successful in developing, along with Steve Feinstone, an assay for neutralization of Hepatitis C based on the ability to pseudotype HIV with the Hepatitis C envelope. That will be really exciting, because no such assays -- It is very difficult to grow Hepatitis C in vitro, as you know.

Assessment of TM-PERT assay to monitor viral clearance -- that was basically showing help across to OTRR to the Division of Monoclonal Antibodies -- and assessment of RT activity in porcine factor, again helping a PI in the Office of Therapeutics Gene Therapy.

Dr. Keith Peden also had a very exciting basic research in identifying the determinant of cell tropin of HIV and SIV, an analysis of relevance of alternative co-receptor for HIV and SIV biology.

I would just like to take this opportunity to introduce to you by cartoon the major findings in the past four years in the area of HIV entry. And

while the CD4 has been identified as the main receptor for HIV more than 15 years ago, it took another ten years for scientists, both at the NIH and elsewhere, to identify the fact that a second receptor, mainly that belongs to the seven transmembrane G protein of the chemokine receptors are important factors in allowing the virus to enter cells.

This is just sort of a cartoon showing how subsequently direction between the envelope and the CD4 confirmation of change takes place. That then allows for recruitment of one of several co-receptors -- here we show CCR5 or CXCR4 -- into the sort of tri-molecular complex that leads to additional changes, eventually allow for an insert of the putagenic part of the gp41.

You will hear later from Dr. Berkower about the work of Dr. Carol Weiss who is interested in this part of viral entry. But both Dr. Keith Peden and myself have focused a lot of our research in the past several years to these additional co-receptors, both in trying to understanding their function in viral entry and what could be the outcome of designing new therapies to target them.

That takes me to my research program: As I indicated, HIV cell entry, studies on the

expression, biochemical properties and function of the HIV co-receptor on primary human cells, evaluation of safety and efficacy of murine monoclonal antibodies, and polyclonal IgG against HIV and its cellular receptors. And I have a long term, ongoing collaboration with Dr. Golding at the Office of Blood, evaluation of heat inactivated Brucella abortus as a carrier for HIV vaccine, specifically for therapeutic vaccines.

In the terms of the co-receptor on HIV reentry, our goal through the past four years was to generate reagents for use in multiple biochemical and biological analysis of the HIV co-receptor, and to study the expression and function of these co-receptor in primary human tissues and cell types.

That included T-cells, thymocytes, dendritic cells, monocytes and macrophages, because we believe studies of the primary target for HIV are the most relevant studies to understand, based on the role of these co-receptors on viral entry and how new therapies or vaccines targeting these co-receptors are likely to work in vivo, and what could be the safety or the side effects that may result.

So the last part is identify the potential benefit and adverse effects of agents targeting the

co-receptor.

With regard to -- The whole question of immunotherapy, as you know, has now come to the forefront, because when they find out that people affected with HIV can control their virus quite efficiently while on highly active antiviral therapy, there is not evidence that their immune response can be fully reconstituted.

A lot of efforts are now targeted to how can we bring back the viral specific immune response. So eventually, maybe we can give them a break for these highly active and highly toxic antiviral therapies and let their immune system take care of the residual virus.

So the concept of immunotherapy and HIV vaccines as the therapeutic agents are very important now, and many investigators try them. One of the main goals of immunotherapy is maybe to bypass the requirement for CD4 T-cells by eliciting helpful cytokines such as Interferon gamma and from other cell types such as CD8 T-cells to induce Il-12 production and improve antigen presentation function of macrophages and to, hopefully, stimulate B cells in cytotoxic T-cells in a CD4 T-cell independent manner.

That's why we concentrated on a bacteria

vector, the inactivated Brucella abortus, and were able to show that is a very good candidate, because it can stimulate both humeral and cellular immune responses in the total absence of CD4 T-cells.

So I would just like to finish this presentation by just outlining some of our sort of regulatory achievements that benefitted from all this expertise that I mentioned to you.

As I told you before, there was, in response to public concern regarding the possible presence of low level reverse transcriptase activity in licensed child use vaccines, including measles and mumps, LLR scientists Peden and Maudru established an improved, highly sensitive PCR based RT assay, and this assay is at least a millionfold more sensitive than the classic RT assays and can detect the G1-10 retrovirus particles of any known or unknown retrovirus from various species.

Very quickly, a panel of licensed vaccines was tested in CBER and five other cooperating laboratories in the USA and Europe, and positive RT activities were indeed detected in all vaccines grown in primary chick embryo fibroblasts, but not in vaccines grown in mammalian cells.

That led our scientists Kahn and Peden to

establish an infectivity assay to show that the chick cell derived RT activity is not associated with the replicating infectious agents, and furthermore, Dr. Kahn with Dr. Shahabuddin demonstrated that even exposure of human cells to measle vaccine does not result in entry or integration of endogenous avian retrovirus sequences.

This work took a lot of time and effort and was very instrumental in the ability of the agency to work with the industry and to determine that measles vaccines are indeed safe and that childhood vaccination should continue.

We also were involved in a variety of workshops in the past several years. We organized a workshop on live attenuated HIV vaccine with emphasis on safety considerations in preclinical studies, which was co-sponsored by CBER, the Office of AIDS Research and DAIAIDS.

We are also -- Dr. Peden and Khan particularly were involved in a DVP sort of OVRR workshop with other members of our Division on transformed cell lines as potential cell substrates for viral vaccines.

This is a very important area that we are still pursuing, because many of these new HIV vaccines

that you have seen in the original table need new cell substrates. Many of them, unfortunately, are transformed cell substrates. We have to understand the risks associated with them as well as the way to show that the risk/benefit is really coming up on the side of the benefit, and the risk evaluation assays has to be developed.

In addition, there was a workshop also that Dr. Peden along with Dr. Andrew Lewis were involved in a workshop on the detection of SV40 sequences in human tumors and, as I mentioned to you, Dr. Peden went on to develop important PCR based assay to look for SV40 sequences in human tumors and other tissues.

I would like to finish here, and be glad to answer any questions.

ACTING CHAIRMAN DAUM: Thank you very much. It certainly sounds like an active group. Are there questions based just on this presentation now? Dr. Faggett, please.

DR. FAGGETT: A question on that very exciting PCR assay 1^{10} particle sensitivity. How soon will that be available?

DR. GOLDING: As a matter of fact, not only it now has been widely available, several vendors