A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:38 p.m.)

DR. KARRON: If everyone would please take their seats. We're going to begin the afternoon session.

We're going to go ahead and start with an introduction by Jerry Weir with the FDA.

DR. WEIR: Is it on? Thank you.

I'm Jerry Weir, the Director of the Division of Viral Products and I am going to give a very brief introduction to the last of our four sessions for this Vaccines and Related Biological Products Advisory Committee.

The topic of the fourth session will be a discussion of the circulating Influenza B strains that you have already heard about today and yesterday somewhat.

As you know, Influenza B viruses are not divided into subtypes, and currently vaccines contain a single B component. There are, however, two distinct antigenic and genetic lineages of Influenza B, which co-circulate. They are designated by their reference strains that correspond to them, and they're referred to as the B/Yamagata lineage and the B/Victoria lineage.

Influenza viruses from each of these lineage periodically become dominant as they circulate. And one of the main reasons that we're here this afternoon is because today and in previous VRBPAC discussions, the question has come up as to whether there should be some consideration given to some alternative vaccination strategy in order to address this issue of having two distinct lineages circulating.

Just to remind everyone, this slide shows the composition, the B-component composition in the vaccine for the last few

years. And if you look to the far right you can see in parenthesis the lineage that each strain comes from. And you'll see that what's happened is we've actually alternated every couple of years with a strain from the Yamagata lineage and the Victoria. And of course, we just recommended that we keep the Victoria lineage for one more year.

So, the reason we're here today, the agenda is as follows.

Besides this brief introduction that I'm giving, our colleague, Dr. Robert Couch, who is on the Committee, has agreed to provide a background to this issue.

And then following Dr. Couch, Dr. Gagneten from CBER will discuss briefly the regulatory implications of any of the alternative strategies that are brought up and that will be presented by Dr. Couch, as well as yourself.

And then we have the manufacturers scheduled to give comments, to get their view

points.

And then we have an open public hearing scheduled after that so that anyone else in the audience that is interested can put in their two cents.

And then what we would hope to have is a discussion among the Committee that will discuss this issue.

So what the goals of the afternoon are, are as follows:

We want to review the available data regarding the Yamagata and Victoria lineages of Influenza B. Discuss the genetic and antigenic relatedness, epidemiology, cross-protective responses to vaccines derived from each strain, as well as the morbidity and mortality associated with Influenza B.

And then have, the speakers will assess the various options to provide vaccine coverage for strains of both lineages.

And then we'll examine the regulatory and manufacturing considerations

for these options.

And what we would like to see the Committee focus their discussion on after everyone has had their input is the following three items, which we can I guess put back up there at the end:

Please discuss the medical significance and concerns presented by the two circulating lineages of Influenza B, and whether such concerns can be addressed by means of an alternative vaccination strategy.

Second, please discuss the feasibility of the various options for expanded vaccine coverage of the two lineages of Influenza B. And you'll see as the speakers go through their data that these could, some of these options will include types of quadrivalent vaccines, supplemental vaccines, as well as some other options.

And then finally we would like you to discuss the possible future steps for both manufacturers and the public health agencies,

keeping in mind of course the context of the global nature of influenza vaccine recommendations and production.

And so that's all I have for an introduction and I guess we can, unless someone has a question, we can move on to our background.

DR. COUCH: All right. Thank you, I'm Robert Couch, Baylor College of Medicine. I was introduced earlier yesterday but not again since then.

I have three introductory comments first. One is I'm your third choice speaker. When Jerry asked me to do this, I said look this needs to be either Nancy Cox or Roland Levendowski because year after year they've presented this data on the lineages and immune responses. And he came back to me and said well Nancy has got a big assignment for the morning, which I think everybody would agree she did have. And he thought Roland had an assignment for H5 yesterday, so I'm not sure

what happened to that one. I said, all right, I think I'm probably a reasonable third choice. So you got the third choice for this one.

Now, the second is I said, he said how much time. I said give me 30 minutes. He gave us 40. So what I did was to add a little bit more, you might say, on the biology of Influenza B, epidemiology, and so forth before we go into the lineage data, which is what we'll have to wrestle with, with regard to discussions.

And one other comment I want to make is my purpose is to provide the background and the options. I won't take a stand. Maybe we'll come to that later on, but the options are for the discussions of the group afterwards. So that's what's coming to you.

And the final comment is in that regard, this has been going on for some time. And I've brought it up on occasions in the

past, but I'm more comfortable saying, not calling this a problem, but calling this a concern. And it has been a concern, and it still is, and it may continue to be a concern that I think needs to be addressed. And that's what Jerry said as part of the introduction here.

All right, with kind of an introduction then, let's go into the subject. Some of this, this is repetitious obviously, but the classification of the human influenza viruses is, and we've already heard A, B, we don't talk about C. It doesn't exhibit that kind of variation that gives us concern. These are our medical problems, A and B, and as you know, subtypes. And within those subtypes, and for B we drift, and that's what the task we have every time we meet here is trying to identify that drift, prepare for it, make the vaccine decisions so it has control.

Now, our current concepts are that these are bird viruses. And they crossed that

species barrier and established themselves in man and that's what we're getting as a problem out here. Whereas, our current concept is that this is a human virus that had our animal origin; we still don't know what it is. So Influenza B are human viruses that we have to live with but share a lot of characteristics with the Influenza A.

And I've chosen to take that tact and a little bit of the background information in contrasting Influenza A. First, just some comments about the virogy.

These viruses have a similar structure. They have the same component parts. They have the same replication sequence. There are some differences, but they're not major ones. But the Influenza B and A have unique nucleoprotein antigens, and that defines them as Influenza A or B, the nucleoprotein antigen, and they are different.

Now, that follows a lot of other differences that are associated with that.

They both exhibit drift, as we said, but Influenza B do not exhibit shift and therefore no pandemic and no subtypes.

Antigenic drift is at a lower rate than that that has been described for Influenza A. And this is from one of Nancy Cox's manuscripts, the evolutionary rate for the HA1 gene and the protein, H1N1, H3N2, and B, and over a lot of years, from 1943-94 here, for the Influenza B, nucleotide changes per site, per year. You see the As are about the same and the Influenza B is a little less than half of that.

Amino acid changes per site, per year, up around five and down to a little over one and a half. And that clearly accounts for some of the differences in the epidemiology between the A viruses and the B viruses as we know them.

Now, a few comments about infection and disease, and in that contrast. There are some differences in substrate

preference. Those that you have worked with these know that B likes tissue culture less than A. A does pretty well with eggs, those vary with time. And the SA performance, whole virus for HI for Influenza B, split products, more sensitivity, A doesn't have that problem. So there are some differences here, but they're all in the laboratory set. But those relate to differences in the infection in the laboratory.

As we know it to have a similar transmission, a similar pathogenesis, a similar infection pattern, and a similar illness pattern, and the same basis for immunity. And it's that we use for the basis for our decisions on an annual basis for the vaccines.

There are some differences in complications but there's a lot of overlap. Both viruses can produce pure viral pneumonia, and both produce, induce secondary bacterial pneumonia. Both produce otitis media or lead

to otitis media in children, sinusitis in older individuals. Acute myositis is thought to be more common in Influenza B than in Influenza A, more in children than in adults, but described for both.

Acute encephalitis or encephalopathy is thought to be more common for Influenza A. The Japanese problem may be a good example, and it's very acute in association with the illness.

Reye's Syndrome, originally thought maybe to be a complication only of Influenza B, it turns out it's a complication, just a little bit more common, it appears, for Influenza B. And both produce various neurologic disorders that we'll call one of the myelitis disorders and there are quite a number of them.

Now, an anecdote on the side. And the reason I like this one, Influenza B and Parkland Hospital 7677. This has Jim Luby's mark on it. Some may know Jim. He's a great

physician. He was a CDC EIS Officer and I have a lot of respect for what his beings, for what was done here and what was said. And this was their experience in that hospital: 15 confirmed cases, three secondary bacterial pneumonia, two with a severe chest disease disorder, and I'm not giving you details on these, high fever and rhabdomyolysis, two cases. Three of Reye's Syndrome, I guess it preceded the aspirin knowledge. Two with neurological syndromes, again, not giving you the details. One Steven Johnson Syndrom. One thyroid dysfunction. One pregnancy with toxemia and two deaths. All Influenza B.

And this is the conclusion out of that, "Quantitatively rare but qualitatively severe, complications and sequelae outside the respiratory system may be the most significant contributors to Influenza B, morbidity and mortality." And I don't think we have a good quantitative understanding for how true that may be, but clearly that is true, just the

uncertainty is the overall significance.

Now, Influenza B is associated with mortality. Here is the data from Thompson, which most of us do. H1N1, H3N2, and B, look at H3N2, you see P&I Mortality estimate, 6,600, 28,000, all causes over 40,000. Influenza A here, H1N1. B is in between. You see 1,100, 5,200, and 8,300, less than H3N2 and greater overall than H1N1.

And this is one of the, this is a period of the epidemiology descriptions in a CDC publication of a ten year period. And it shows the circles, which they sometimes use. The size of the circle was the magnitude of the epidemic. And the viruses are the pieces of the pie. The slash marks are Influenza B. You see, here is about three quarters of them, Influenza B, a small number, and Influenza B epidemic, a sizeable one. Mostly Influenza B, but a small one. Influenza B almost half of a big epidemic. Influenza B, three quarters of a major epidemic. So that was actually four

out of the ten years there, which is a little more common than most of us think of it, but a significant cause of epidemics for influenza.

These are age distributions. I know, and I think most people that Influenza B is more common in children. This is the kind of data that is the source of that generality. This is data out of Houston. Two successive epidemics, A/Victoria and the next year we had a B/Hong Kong epidemic. 1,100 isolates in this one and 670 isolates in this one. See, 0 to 6 months, 7 to 12 months, 1 to 4, 5 to 9, so on down the line, 45 to 64 and greater than 65.

If you look at Influenza A, you see that this is what gets you right away. It's all running about the same. Seven, six, seven, two, and this seven if four, versus the distribution, 100 percent is the total obviously. This one, and here is nine and five, which you see thirteen percent, eight

percent, and then when this 30 percent grabs you. So if you look at five to fifteen, half of the isolates in the Influenza A, in the Influenza B outbreak are in that age group, a much higher frequency, lower and higher, and a greater distribution for the Influenza A epidemic.

That's the kind of data that leads to the association that it's more of a problem, not more of a problem but a major problem among children.

This is also, I experience in looking at, these are low-income clinics, charity clinics and private hospitals and private physicians offices. Just looking at the children, look at the low income. You see I put the distributions to the total here, 12 percent, 3 percent, 30 percent, 15 percent. 38 and 46, so it goes up here, and it's high down here. I dropped this one just because you can argue in the low income groups that we're getting an age group where it's hard to

control the children, even get them to the doctor. But if you just go up to age 9 and take this group, you see, three quarters of those isolates in this group, a quarter of them under age five, whereas half of them are in the low income age group under age five.

That's been not an unusual characteristic, and it's also true to the certain extent to Influenza A. But they spread more and the rates are higher among low income groups. We can speculate as to the reason for that.

Hospitalizations for influenza virus infections, 1969-1995, and this is Simonsen's data. Only 1 H1N1 epidemic, but hospitalizations, you see, look at H3N2, 12 epidemics, estimated 85 to 220,000 in excess. Influenza B isn't the highest, didn't even get close to the lowest. So a much lower hospitalization rate.

On the other hand, if you get put in the hospital, this is the data out of DC

Children's Hospital over a number of years, 131 Influenza As H3N2 isolates, 54 isolates of the children admitted to the hospital. Syndromes, upper croup, bronchiolitis, and pneumonia. And you see they overlap. They're both here. So you get croups a little higher than Influenza A, and other people have pointed that out. But if the child gets sick enough to put in the hospital, it's the same disease that you can see in an Influenza A infection.

And then go back to another age group so we don't forget the elderly. An outbreak in Influenza B nursing home, 1979. This represented an antigen change. I didn't look it up, but I presume it's probably the B/Singapore/79 change, which was one that was recognized. Nursing home, 359 cases, 129 yield a 36 percent illness rate, 5 hospitalized and one death. 93 percent of the individuals had been vaccinated, but there had been a significant change in Influenza B that

caused that outbreak and then related to this occurrence in the nursing home.

So I would summarize the features of the Influenza B epidemiology as we know them today here. The major cause of an annual epidemic, about every two to four years. Infections occur in all age groups. Illness is most prominent among older children and young adults. Illness in infants and young children appears to be more common among the low income groups. Infections are prominent in the elderly in some epidemics, with excess mortality, but not in all epidemics. Overall impact is less than H3N2, but greater than H1N1. I think that's a fair statement that we would all agree with. But overall, Influenza B is a significant cause of absenteeism, clinic visits, hospitalizations, and deaths. And that's a reason Influenza B is in the vaccine and one of our considerations that we addressed this morning.

Now, if move on to the lineage

subject, this is a, Nancy showed you one this morning, this is one from last year, but just to remind year that there are pretty clear cut change and differences in ferret sera. And you see here is a B/Yamagata lineage and a B/Victoria lineage. And we're coming up here, I'm not, I chose to just stay away from all these strain names. So what you're going to see is the lineage, B/Yamagata, B/Victoria, not the particular strain that represented that lineage in any given data. So I think it'll be a little bit easier for you to follow that way.

And this is a description of the sequence as it's generally known now. Now, before the 1980's, Influenza B was considered to be a single dominant strain in the epidemics, each year and in epidemic years.

In the mid-80s and early 90s, B/Victoria/87 like strains were dominant. B/Yamagata was present, however. It was recognized, some of it in retrospect

recognition.

In the early 90s to 2000, B/Yamagata like strains were dominant, except for Asia, where they had both of them, B/Yamagata and B/Victoria.

2000 to the present, both lineages worldwide. That's the major reason for our addressing the topic today.

And another example, this was presented to this Committee in early January, at the January meeting in 2000, and I'm sure it was probably was Cumiac Nairomi. But they had had a major problem with B in two previous succeeding years, and this was the example of what we're seeing in Asia.

Here is the Yamagata derivative. That was their vaccine. Here was their outbreak two successive years with the B/Victoria. And they were, basically as he described it, smashed with Influenza B infection and disease.

And his summary and

recommendations I thought were interesting. For the B components, should we consider B/Harbin, that's a B/Yamagata strain, B/Beijing, a B/Vic strain, or a third strain which efficiently covers the above two strains. You see if we had that, we wouldn't be having that discussion at all and our decisions would have been easy every time the subject comes up. So the question was raised but we don't have the solution to it, unfortunately.

And I like this recommendation from 1999-2000 recommendations from WHO. For Influenza B, either B/Yamagata or Victoria depending on your local conditions. They just putt and left it up to the individual countries to decide what they were going to do. They've not done that every year, but they sure did it that year.

And this is the circumstance before we started getting a little more concerned of this problem. Here is a

geographic distribution, October '97 to 2000. This is one of Nancy's maps. And here we are in the Far East for Influenza B, you see, and the rest of the world blank. And then in late-2000 going over into 2001, then it started changing. Here is Asia. Here is Italy. It began to show up in parts of Europe and in North America. So then we began to see the Victoria lineage appearing. It was here around the late-80s and 90s, but reappearing in the Western Hemisphere.

And this is my table of the distribution of the lineage starting in '98-'99. Now, this comes from that stack of things on my filing cabinet behind my desk. And there are differences in the numbers here, and the reasons are, for a number like this, for example, I had the report from the full season. From a number like this, I only had a report that was given out at this meeting, for example, you see, in February. So they're smaller numbers. But when I had both, while

the percentages are different, the patterns were the same. So I think we're all right with pattern thinking rather than necessarily the harder percentages.

And I chose to star those in which B was equal to or greater than 20 percent of the isolates. Well, that's a little bit arbitrary but in my mind when you get over 20 percent now, that's a significant contribution to the epidemic. So you can see the ones that are starred here.

So we go up here to 1998-1999, 100 percent Yamagata, and the vaccine that year was Yamagata. The next year, 100 percent. The following year, 100 percent. And then a B/epidemic, a B/contribution of significance and Yamagata vaccine. And then you can see then, then the B/Vic, we're talking about U.S. now, then the B/Vic appeared. And it was not significant that year, so we switched to a B/Vic vaccine, but we had a B/Yamagata dominant. And then we go with a B/Yamagata

dominant the subsequent year and went back to a B/Yamagata vaccine, and now we have a significant contribution from Influenza B, and most of the isolates matched the vaccine.

B/Yamagata the following year, but now we have a Victoria predominance. And so this year it doesn't reach that 20. It's running around 17 percent, but two-thirds of Victoria, so at least yes, no. It's Victoria vaccine, but I didn't get it starred, that's it. But the Malaysia is matching at this particular point. So when it started circulating, we got two right and we missed on two.

And this slide does a good example. Nancy gave this one to us last year again. And I like to use this to say that this is a good example, I think, of the fact that these two lineages are jocking for dominance, and it comes and it goes in different parts of the years and has been coming and going at different parts of the

world.

Now, what's going to happen? Is this temporary and will go away or not? Well, we don't know the precise answer to that, but this manuscript relates to that question.

Multiple Genotypes of Influenza B Virus Circulated between 1979 and 2003. This is an article out of the Memphis Group. And they completely sequenced 31 viruses. The lineages, according to them, were established somewhere around the mid-80s. It had been suggested by the CDC folks earlier that it was around 1983. There is other data centers, probably was close, sometime in the 70s, at least 1975. It may have been even earlier than that in which the lineages started separating and both started occurring. But by 1980, or shortly thereafter, it was pretty clear.

And they used as a parent a Russian strain showing the two lineages clearly are moving away from that. And

calculated again evolution rates. This is, this is, this is a little bit higher than the one that had been seen by Dr. Cox, a little bit low, but see, at least suggested B/Yamagata, it may be a little bit more commonly changing than the B/Victoria and the same for the amino acids.

And you could get the impression, when you look at this data, that B/Yamagata looks like it's a little more likely, a little bit more of a dominant lineage, and this would be compatible with that but certainly not in enough data for you to make any kind of conclusions or any kind of planning on that basis.

And they agreed with other individuals looking at the same subject that the Influenza B had been undergoing a great deal of reassortment, mixing up all kinds of genes. And out of those 31 sera types, 31 viruses, they had 15 genotypes. I mean basically one out of every two was a different

genotype.

Unrestricted mixing of lineage genes, they could find no paired relationship basis for them and so their conclusion had to be no survival advantage to either one of these lineages. So we don't come out of that with a feeling that one is about to move and replace the other, or any kind of our feeling or thinking we sometimes use for Influenza A.

And here are the genotypes, the 15 genotypes. Here is the Russian. Here is Victoria/87. There was an 85 virus that was identical. Here is Yamagata. That has a shared nuclear, a non-structured gene here. And there was a virus in Memphis that has all eight that appear clean. That's somewhat later. But you don't need to go, you can look at the stripes just are all mixed up there. It didn't appear to be any preference for any of these sorted out with any of the others, so they just concluded we can't, we have no idea what kind of virus is going to be showing up

with the future. And that included the hemagglutinin genes, which of course is our focus.

Now, the problem with this is only 31 viruses. And this, I think, is important to be followed, in my view, as to what, is this prediction and anything that would say it's not right so that we would say these co-lineages are likely to continue.

Now, we just had a press release that NIAID had now completed the sequencing of 2000 influenza viruses, of gene sequences. And we sent 50 Influenza B strains over a ten year period to them for that purpose and I'm sure a lot of other people did as well. Somebody needs to examine that data bank now, and if that confirms the conclusions from here, then you would have to conclude these co-circulation is indefinite, in the indefinite future. And that's an important bit of information that would relate to any decisions that we'd want to make. So that

would be one of my recommendations on data if we get to that point.

So here's a summary slide of the B Lineage surveillance data. Two distinct antigenic lineages of Influenza B have circulated at least since the mid-80s, probably before that.

Both lineages have circulated in Asia since emerging.

The B/Yamagata lineage predominated in North America during the 90s. The B/Victoria lineage was essentially absent but was in Asia.

Co-circulation of two lineages has been present in North America since 2001 with varying dominance.

And the available data currently suggests that co-circulation is likely to continue. And as long as we have co-circulation, we are no better off and we can't predict which it will be I think. It will be a guess.

Now, let's look at some of the antibody data that relates to the decision-making to this body. Serum HAI antibody after an inactivated influenza vaccine, and this is data presented at this Committee. Rather than present all these different strains, I did make selections. And I will say, I will claim they are only representative because you look at them, the titers and frequencies differently when you use them with different strains, but the patterns are the same.

B/Yamagata 1988-'89, adults and elderly, you see, the number, somehow this group seems to like 24. I'm wondering why not 25, but any rate they like 24.

B/Yamagata like, you see, percent rise, GMT, and percent equal to or greater than 40. So if you just look at this one, you see, 75, 178, 97 percent equal to or greater than 40. Elderly, somewhat lower, 97, 67. Somewhat to be expected.

Now, go over to the Yamagata, we

follow the same thing. If you just look at the last column, it displays the problem, 100 percent, 75 percent to the elderly, 8 percent, 75 percent for the elderly.

Now, if you look at the opposite lineage not in the vaccine, you see, let's just, let's me, let's just take the equal to or greater than 40. It illustrates the data. 97 percent equal to or greater than 40, down to 59 percent. 67 percent down to 25 percent for the opposite lineage. Same here, 100 percent, 33 percent, 75 percent down to 17 percent. 88 percent, 38, 75 down to 50. See, a significant drop in the coverage for the opposite lineage.

Now, here's a B/Victoria vaccine, in which we've got 88 percent here, 75 percent, slightly lower in the elderly. You look in the reverse direction, now it's 88. I dropped to 64. 75 and I dropped to 63. So the patterns worked in both directions. And the reason for showing this one separate, the

2004 and 2005 vaccines is this one now has children stated, children sera.

Adults again, and we see the same pattern, you see, a B/Yamagata vaccine, 94 percent, 57 percent in the elderly. You go to the opposite lineage, it drops 94 to 46, 57 to 40. The same down here if you do the adults, 96 percent drops to 38 percent with the opposite lineage, both the Yamagata vaccines.

Now, let's look at the children. 264 sera, I wondered myself how they all of a sudden had that many in one year, but 264 sera. 79 percent rise, pretty good for the 5 to 8 year olds. 48, GMT, 64 percent, not bad at all, you see, we think, most of us think of these as less than a normal adult and elderly less, children are less. And that fits with that generality.

But if you look over at the opposite lineage, it's a much more of a drop, 8 percent. If you look at those, half, 6 months to 2 years of age, see we're looking at

only 9 percent got equal to or greater than 40, and 0, nothing basically measurable to the opposite lineage in that particular age group.

And these children I don't know the ages of them, but you see the same general pattern here is 40 percent equal to or greater than 40 to the vaccine antigen and nothing measurable, presumably in any, among the children to the opposite lineage at all. So it really looks terrible for very young children.

Now, I'm sorry that the rest, the other half is not available for this data, which I put in and might not have if you hadn't sent us these articles. I had forgotten about Jan England and the two articles out of Seattle. But one of the points to make is that that previous one, see this one right here, 10, 9 percent, 0 percent. That is the same vaccine you're looking at here, which is now 62 percent GMT and 88 percent equal to or greater than 32. It's a

different group of children, maybe a different vaccine, a different laboratory; in fact, we all ought to contract with that laboratory to test our serology maybe. But again, some of the variability that you can get in things.

Not quite as good with the B/Vic strains, but not bad for very young children. And these were very young children. They were all between say 6 and 23 months. So it's not always bad, but we don't have the opposite lineage data from that particular one.

And this last one is the summary of the work data that I had from the WHO reports, '98, Al missed a year too here. But four Yamagatas, a Vic, and a Yamagata. And if you look at equal to or greater than 40 and equal to or greater than 40 from Vic, which is the way to express your data, here is the drop across the board in the elderly, which you expect to see. And B/Vic, you see, now we're 79 percent to 39 percent. It drops to 30 percent or so in the percent of individuals

what some people call protective titers. And children only in this last one, 13 percent equal to or greater than 40 to the vaccine lineage, and 40 to the opposite lineage.

So a little inconsistency, but by and large, very young children get very negligible benefit for the opposite lineage of the Influenza B that's in the vaccine.

And this is another. We heard from, Dr. Ye showed us that I've sort of gotten used to seeing some of this data now. What percent lower in those GMTs, you see, and most of us think in terms of roughly a two-fold different in GMT is getting at the area of significance. And they quoted in percentages, you see, so these would each be 50 percent or greater reduction for that opposite lineage for that particular individual. So those are the kinds of figures that we have to deal with.

Now, the summary of Influenza B antibody responses. Antibody responses among

healthy adults to the vaccine like strains are generally good.

The antibody responses among the elderly to the vaccine like strains are reduced compared to young adults, but that is data we're custom to seeing.

Antibody responses among children to the vaccine like strains are reduced compared to adults, particularly in young children, again data that we're used to seeing, but maybe particularly, but particularly among infants.

Antibody responses to the lineage not in the vaccine are significantly reduced in all age groups. That's my judgment of significance, not a statistician's judgment. But I would consider it clearly clinically significant compared with the vaccine strain responses, and they appear to be minimal responses in very young children.

Now, one of the questions I ask is if we use the live vaccine in children,

FluMist, does it do better at crossing that lineage. And I can only give you a little bit of information. I know Kathy Choeling is in the audience and I spoke to her a little bit earlier, and I think she can elaborate on these. But I got Arnold Monto to send me his data, this recent publication in the New England Journal of Medicine. And these are young adults, or 18 to 46, with a mean of 74, got live or inactivated, 278, 273, equal to or greater than four-fold increase with the Yamagata lineage, which was the vaccine, or the opposite lineage, equal to or greater than 1 to 32. And you can see the kind of data we just got through looking at for the inactivated vaccine, 85 percent, 30 percent for the opposite lineage, 98, 73.

Now, if you look at the live vaccine to only 12 percent had a response to the vaccine lineage, but four percent against B/Vic. And these ratios are basically the same.

If you look at these, this one is down about 25 percent. This one about 20 percent. But those are in the same pattern so that doesn't support any particular advantage for the live vaccine.

And this is the other source of data that I have, and that's the recent publication by Bob Belshe in the group on basically -- but the huge multi-center, multi-country study. And now, was the virus well-matched, no placebo in this study, you've either got live or inactivated. Here is the attack rate. Virus-positive illness was inactivated, live, and at 27.3 percent reduction. Not statistically significant, but reduced when the vaccine, when the infection virus matched the vaccine virus. Now, their definition of non-well matched is the opposite lineage or a B/Yamagata, which is significantly different. It's not defined in the manuscript what significantly different consisted of. But it probably doesn't really

matter because when you look at that whatever poor cross-benefit you got from inactivated, which would be our concern, live is no better. So this is, there is no data here to support the live vaccine being better at crossing that lineage than was true for the inactivated vaccine.

So, with that as a background of information now, let's move on to consider the options. And the options were handed out to the Committee, and I added one to that list of options, which seems to me is fairly obvious, as I told you earlier, really we should've stuck it there probably to begin with.

And that is, don't change anything. So that is the first one up here. Continue the annual trivalent vaccine and do the best we can, which is what we got through doing this morning.

The advantage of that are a system is in place for each step to delivery of the vaccine. A single strain selection is made,

reagent preparations, and manufacturing, and the delivery of that vaccine is, and the manufacturing and everything would be unchanged. See, once you have something in place it is tempting to leave it alone.

The disadvantages of that would be co-circulation would leave a proportion of persons unprotected. We've already talked about that. Children and elderly perhaps at the most risk for being unprotected. A major mismatch then would result from selection error, not from a novel virus emergence, which is the way we usually think, that we miss when a novel virus emerges like we had the discussion a little bit of H3 this morning. Those have been the -- in this case we might just make a bad selection. You hate to think that way. And then you end up missing and have significant disease that cause dyslexia.

Option two, and I added this one to the list, alternate annually the lineage strain in the vaccine. And the way I said

that to Jerry, that's why I had a little less concern this past year or this current year than I had the previous year because we changed lineages.

And the advantages would be it would ensure protection to both of the lineages, at least to some degree, a little quantitative uncertainty there, among those who are vaccinated yearly, because you're switching yearly, your prime, you're boosting. It requires only one antigen selection, where we are right now. Reagent preparation, manufacturing would continue the same system we have at present. We'd be switching Bs every year, but we'd be close to the same system we're working with at present.

The disadvantages are we have the potential from reduced protection from a mismatch. We'd have to concede that. We have that now when we miss, when we don't guess correctly. And we'd have the potential for the reduced protection for those skipping a

year. A number of individuals don't get their vaccine every year. You see, if you've got the two lineages, this one and one in the middle, you might be in trouble for that lineage. Not a half frequency, I don't think, but it clearly occurs.

Options now, here's a third option. Quadravalent vaccine with 15 micrograms of each lineage.

The advantage to that would be the expected responses to both lineages should ensue. And it should provide the expected protection for both lineages.

The disadvantages would be the possible increased reactogenicity. The total dose would be 60 micrograms. I think that would be negligible as my personal opinion, and certainly not a reason it, it could be evaluated, but not a reason for serious concern.

It requires a selection of two strains now and the reagent preparations

yearly. So that compounds the problem at the decision level where we were this morning and at the reagent preparation at CDC. And the manufacturer, if he doesn't tell me that going to create a problem, I'll be terribly surprised. The lack of data on responses to a quadravalent vaccine, we would always consider that something of a deficiency though we would think it should be good. And my, this one is personal, I personally have a little problem with Influenza B then becoming the dominant vaccine component with 30 micrograms when the dominant vaccine component consideration should be H3N2. It's a little bit of the same idea that we heard this morning.

And I thought there was a third example, but whatever I had in my office I couldn't find it anywhere.

Vaccination with two strains, 1956-57, both B/Lee and B/Great Lakes were added to the vaccine. 63 and 64, both B/Great

Lakes and B/Maryland. 73-74, B/Mass/71 and an additional monovalent B/Hong Kong/72 was made. I had no idea when it showed up, how well it was used, or that thing, but was added when this change antigenically occurred, which caused a major B-epidemic the subsequent year. So that supplemental vaccine was added.

The fourth option, a quadravalent vaccine with seven and a half micrograms of each lineage.

The advantages were if the response to both lineages should ensue. The overall B dosage would be unchanged, 15 micrograms. The reduction in immune responses and protection, versus 15, should be minimal.

The disadvantages are that it would reduce the usual dosage of the single most-likely antigen, which is a fix, to a great extent in our thinking. Some reduction in immune responses would occur and some responses in protection is possible. It would require the yearly selection of two strains

and reagent preparation. Would this give the manufacturer problems or less so than 15. And lack of data, again, on the quadravalent vaccine.

Now, this is data to support that perhaps being okay. This is John Treanor's publication. And groups getting the full dose and half dose, and this is Influenza B, 2002, this must've been five years ago, the actual state, one of those shortage years when the half dose study was done.

The vaccine group, prior vaccinated group and no prior vaccinated increased four-fold you see. A significant increase, just 10 percent significant for a four-fold increase. And the same here, the 84 versus 73 percent. No differences in the GMT. No differences in the percent equal to or greater than 1 to 40. And if you look at this reverse accumulation of individuals, here I even forgot which one was which. But here is the full dose and the half dose among those

who had previous vaccine. We do see decreasing numbers of 1 to 40, 1 to 80, 160 and so forth, and of those with no previous vaccine. So in that study, in healthy adults, there's a negligible difference between some slight reduction if you only gave a half dose if it's minor. The children, the data you'd like to have for more confidence are, however, is young children, and we don't have that data.

Now, the fifth option, both a trivalent and a quadravalent vaccine, so to reduce the magnitude of what you're proposing be made would be the reasons for this.

The advantage would be that there's a greater need for children and probably the elderly in which the quadravalent would provide that. The expected responses to both lineages should follow the quadravalent. The quadravalent should provide expected protection from both lineages.

The disadvantages to this would be

that those given the trivalent may have reduced protection against the opposite lineage. And the available data suggests that all ages would benefit from that quadravalent, including those healthy adults. There were possible increased reactogenicity. You've already heard me for the quadravalent, I think, would be highly unlikely. It requires yearly selection of two strains, manufacturer problems, lack of data on the quadravalent, and again, an awful strong emphasis on Influenza B rather than H3N2, which I personally have a little problem with.

And the final option is production and delivery of a supplemental B, 15 micrograms it would be for the other lineage.

The advantage would be again the expected response you should get to both lineages should provide the expected and desired protection.

The disadvantages would be required, again, two strains to be done. The

manufacturing problems for the supplemental vaccine, delivery problems, it makes Influenza B again the dominant antigen, rather than H3N2. You keep hearing that from me. But this would complicate delivery too, particularly for the unprime. Now we're talking about three doses, maybe even four injections depending on what you need from that opposite lineage. And it brings up the question of having to now really seriously consider adding spring vaccination, which has been proposed as a way to shorten what we have to do right with two doses in the fall. So there are some disadvantages associated with that one too.

Well, that was my assignment and the preparation I presume for the discussions.

DR. KARRON: Thank you very much. Next will Sara Gagneten from the FDA.

DR. GAGNETEN: Hello. I'm Sara Gagneten. I'm a Scientific Reviewer in the Office of Vaccines. And I didn't request for

an extension of my presentation. I'm going to very briefly give you an overview of some of the regulatory considerations for the alternative vaccine options that Dr. Couch talked about just now.

The biology of Influenza B, Dr. Couch just went through it briefly just now, went through it very, in detail, and just wanted to mention in this slide the problems of coverage.

Starting in 2002-2003, as Dr. Couch mentioned, the vaccine, it was recommended that the vaccine contained strains from the B/Victoria lineage.

That year the majority of Influenza B viruses isolated in the U.S. were from that lineage, so the strain was retained the following year in 2003-2004. But that year, as you see, the majority of the viruses isolated in the U.S. were from the B/Yamagata lineage.

So for the following year, 2004-

2005, there was a switch to the B/Yamagata lineage. And then that year things worked well and the virus was retained in 2005-2006.

But then the following year, the majority of the viruses isolated were from the B/Victoria lineage. And so this, as you can see, this slide illustrates problems of coverage that we've been talking about every two years, well, I mean, it's been happening every two years but that's coincidence.

So some of the, okay, I'm sorry. So I will talk to you briefly about the alternative vaccine formulations to expand coverage for circulating strains. And I will discuss the regulatory passageways for licensure of alternative vaccine formulations, manufacturers using this license process.

Just as a refresher I wanted to mention that each year after selection of the strains, manufacturers submit a BLA supplement to their licenses and that supplement does not contain chemical data.

Also, as a refresher, their license vaccine contain influenza viruses from two type A strains, one type B. They contain 15 micrograms from each strain for a total of 45 micrograms of hemagglutinin per adult dose.

So some of the alternative vaccination strategies were just mentioned. I'm just mentioning these three that would require some kind of licensing action.

So the option, one option would be to include, to develop a quadravalent vaccine with two type-B strains and two type-A strains at 15 micrograms HA for each one of the strains and a total of 60 micrograms HA per dose.

An alternative would be to develop a quadravalent vaccine with half the amount of HA, or 7.5 micrograms HA for each of the two B-strains and 15 micrograms hemagglutinin for each of the A-strains, for a total of 45 micrograms hemagglutinin of the monovalent Influenza B vaccine that would be administered

with seasonal trivalent vaccine.

Now, for the regulatory considerations for alternative vaccine formulations. When you factor using a license process, I wanted to mention that at the clinical level the quadravalent vaccines would require clinical immune response and safety data. And the monovalent Influenza B vaccine administered with seasonal trivalent vaccine would require clinical immune response data for administration to address issues of possible immune interference.

At the manufacturing level, the applications would require data for each virus strain as it is done annually. And in addition, we would need data for steps that differ from the license process, the manufacturing steps, such as formulation that would differ.

Lastly, administratively, the type of application that would be required, there could be a clinical supplement to an existing

BLA or a new BLA is under discussion in CBER. And options related to trade, a change in trade name, surveillance, considerations impact the type of application that would be required.

Lastly, we would require revision of the labeling.

I will conclude, and this is just to mention a few of the advantages and disadvantages. Dr. Couch went through it in detail, but generally, these options would represent an improved coverage against circulating influenza strains. They would also contribute toward preparedness of possible introduction of previously circulating strains, such as H2N2.

And the important disadvantage is, as you've heard from this morning, formulations that contain four influenza strains may cause manufacturing constraints that may affect the timing availability of vaccines.

So with this, the topics for discussion will come after the next topic.

DR. KARRON: Thank you. I think we'll move on now to comments from manufacturers.

Dr. Colgate.

DR. COLGATE: Good afternoon. My name is Tony Colgate. I'm from Novartis Vaccines based in Liverpool. And I was nominated by the former working group to give this presentation on behalf of the industry. And although you see the Novartis logo on the slides, it's not totally a Novartis presentation. There was input from all of the U.S. manufacturers, and indeed you'll see that the presentation is actually based on the presentation that was given by Al Thomas from Sanofi this morning. So basically I'm building on his presentation.

I really just want to set the scene initially. I personally find the influenza vaccine the most stimulating vaccine

to manufacture. The main reason for that is it's a seasonal product. It's invariably a new product every year and, therefore, a new challenge. We have a liberty production period, so you get your product to market on time or you don't sell it. And it's changed by the next year, so it's lost.

And at present, all the influenza vaccines are derived from virus inflated in eggs. So basically that's all I'm going to talk about today. And the majority of FDA approved influenza vaccines are inactivated. And that's for all except for the MedImmune cold adapted live virus vaccine.

And many of the issues that I'm going to talk about here actually don't apply to that vaccine, but I'm not going to address those, but I think Kathy is here if you want to talk about them.

You saw this this morning. Basically, I put it up and you're going to see it twice more later on to emphasize that we

have this fixed period really from somewhere at the beginning of the year, manufacturers start manufacturing at-risk, to the strain decision time, to August, in which we have to produce an antigen. And this again is assuming that in fact we have two, two seeds, or two strains that are known and only one working seed was to be produced.

A number of things are outside our control. One is the virus reference strain, which we have to, we have to get from WHO-approved laboratories, reassortant production, and also reagents. So basically it's not totally under our control. And really getting the vaccine out is a collaborative effort between industry, and WHO, and the WHO-labs. And in general, it works very well.

So we have to produce our three lots of antigen in this period, produce reagents, and then we have to fill, and formulate, and distribute.

Now, I put on the top here just to

kind of remind you it's a seasonal product, new product every year, and limited production. So there's pressure on all the time.

Now, the growth potential of the seed virus, as Al said this morning, the quantity of monovalent influenza vaccine that can be produced is limited by the least product of the monovalent strains selected. So basically if you put an extra strain in there, we've got another constraint.

And each working see requires at least four weeks from receipt of the seed to develop prior to using in large scale manufacturing. Now, every monovalent that we produce has a minimum quality assurance requirement. We have to do virus inactivation validation qualification on each strain, process validation qualification, assay validation qualification, and we also, one of the manufacturers has to produce a purified antigen for the single radial immunodiffusion

reagent.

Now, the potency test reagents are most important to us, as you've heard before. We can't formulate trivalent vaccine until we have some way of standardizing the vaccine. So they're required to determine the potency of the monovalent.

And, again, as I've said before, this is not under our control entirely. We are relying upon control agencies, CBER, in this case, to produce, standardize and supply reagents for all new strains. So basically not only will there be more pressure on industry, there will also be more pressure on CBER.

And as we've said before, production begins at-risk prior to the mid-February decision. If we don't do this, we are endanger of not producing sufficient doses. And as we already know, one strain is usually produced at-risk. I don't think I need to dwell on that. We covered that well

this morning.

So I've got a look at a couple of scenarios and I don't think I've covered all the scenarios that Bob Couch suggested, but I think I've got some of them. Basically, the brief I had was to look at a vaccine containing 45 micrograms, which is basically what the trivalent vaccine contains now, and the vaccine containing 60 micrograms.

Now, for 45 micrograms, there are two options. One is 15 micrograms of the A-strain and seven and a half of each of the B-strains. I've heard that discussed many times in the past, but I was interested to see actual clinical results. I didn't know there was any clinical data on that.

And the other is, could be to put in approximately 11 micrograms of HA of each strain, but between 15 and 20 years ago the vaccine actually used to contain 10 micrograms of hemagglutinin, but that was changed in preference for 15 micrograms. And I'm not

sure that anybody will want to go back on that.

And both of these formulations I thought may have clinical challenges with lower HA content per strain.

The other alternative is a vaccine containing 60 micrograms in total, 15 micrograms of each strain.

And another alternative we have is to reduce a monovalent B-strain in addition to the trivalent vaccine.

If we look at the first scenario, the good thing is that we could potentially produce the same number of doses as the trivalent manufacturer. But again, as I've said before, it's subject to the growth characteristics of the fourth strain, or the strain which is the lowest yielding. But what we would have to produce is initial B-strain seed and that would require manufacturing and testing. And as I said before, there would be the additional testing for the fourth strain

regarding virus inactivation, process validation, assay validation, and production of the purified antigen for the reagents. And this of course would, as I said before, give additional work to control agencies.

Possible difficulties that certainly our policy control people perceived when I was discussing this with them, they were worried about the accuracy of the assay with two B-strains. They have not looked at that before. They were worried that there might be symbiosis during the two B-strains and that it would be difficult to accurately measure them. But this presumably would be down to specificity of reagents. And that's something that we would need to consider if we're going ahead with this.

So basically this is the same picture as before, except we divided the third, or divided the third part into a three and a four. So basically we're using the B-slot to produce two halves of the B-strain

containing seven and half micrograms instead of 15.

The second scenario with a 60-microgram HA total vaccine is a different situation. And assuming that there were no changes to manufacturing capacity and timing of strain notification, we could only produce 75 percent of the doses compared with trivalent vaccines. So this has a significant impact.

And as you'll see when I put the chart up again for the third time, you'll see it may require productions of two strains at-risk because of the shorter periods. We may have finished, run out of steam on the first at-risk production before the strain decision is made. And also balancing of the four strains would be more difficult at the end.

There would be the additional work, as for the first scenario, which is the production of the new strain, additional testing, validation, qualification, more work

for CBER and possible difficulties for two B-strains to be assay.

And here we are, as you can see, with a smaller slot here, we may be in a situation where we are looking for the second strain to manufacturer before the first one. There may be ways around that, but I guess that would require some pre-notification of A/B strain before the February decision.

Now, again, assuming no changes to manufacturing, and capacity, and timing of strain notification, if you try to produce an independent B-strain, this has even more adverse effect if you're trying to vaccinate everybody with a trivalent and a monovalent because it requires two vials of, one of the trivalent vaccine, one of the B- for every vaccination. And that would reduce filling capacity by 50 percent if a second strain is not identified very early.

If only subjects were to receive the monovalent B-vaccine, i.e. children, then

the impact on monovalent strain manufacturing depends on the size of the population selected. You need to identify timing for vaccination of the selected populations, still a potential impact on filling capacity and therefore, a potential impact on the number of those who supply.

All I'm considering here are really basically the mechanics of doing this operation. I haven't considered any clinical requirements, regulation, or legal pathways, which I think have been covered previously.

And it may require a timing of strain recommendations for all the four strains. An earlier recommendation may be required if we're going to get the required doses and number of doses. But you suggested that maybe we could produce the fourth B-strain out of season. That would require some kind of decision in advance of which strain that should be.

In addition, as we heard

yesterday, most manufacturers are now actually producing H5 antigen during the closed season. And in Europe, vaccine manufacturers are actually producing for the Southern Hemisphere in the down season. So that suggestion is a little bit limited, but it's worth discussing.

Just to mention, we, obviously, cell culture is the flu product of the future. And multiple manufacturers are working on cell culture influenza vaccine, but at the moment none is approved in the U.S. or I don't think anywhere else either. But it's getting close, I think, in Europe.

Cell culture has production attributes that may facilitate manufacturing of a tetravalent vaccine, but that has not yet been established.

So in summary, all of the scenarios that I've discussed increase the workload and complexity of a season of product. That potentially changes other year and is subject to exactly manufacturing time

constrains.

The second scenario, the 15 micrograms of each strain, the 60 micrograms of HA total would reduce existing production approximately by 25 percent, assuming no changes are made to manufacturing capacity and the September release, because the release date is dependent on the date the virus seed is supplied, growth rates, and yields, as already described. But this could be overcome with a corresponding increase in production capacity, but that means planning and time.

Production with addition monovalent vaccine B-strain is also likely to impact on vaccine supply.

So, in conclusion, influenza vaccine manufacturers is complex, increased complexity with a four vaccine strain, and the balance between the supply and timing to deliver with additional strains.

Having said that, if desired by health authorities on the basis of public

health need, the vaccine industry is prepared to try to resolve the many issues together with health authorities.

Thank you.

DR. KARRON: Thank you, Dr. Colgate.

Next on the agenda is the open public hearing.

Christine?

MS. WALSH: As part of the FDA Advisory Committee Meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the Committee.

I have not received any requests at this time.

Is there anyone in the room who would like to address the Committee?

(No response.)

Dr. Karron, would you read the

open public hearing statement please.

DR. KARRON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session at the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the top of this meeting.

For example, the financial information may include the company's or group's payment of your travel lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at

the beginning of your statement to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. CHOELING: My name is Kathleen Choeling and I'm an employee of MedImmune. What I wanted to do is just follow-up on, to provide a little bit of additional information on the immune response, the cross-lineage reactivity following vaccination of children with FluMist because there have been a lot of questions, I know, following some of our findings that show we have broad cross-reactivity against drift strains within a lineage.

There were some question whether that would extend across the lineage. So what we did is look at a few different pieces of pertinent information. And to summarize it

before I tell you, it basically agrees with everything that Dr. Couch summarized so nicely earlier. But I wanted to just reinforce that.

The first thing we look at was the response in ferrets. And when you vaccine ferrets with FluMist containing one Influenza B lineage, there is no immune response developed in the ferrets to the opposite lineage that's not in the vaccine. If those ferrets are then challenged with either lineage of B-virus, there's complete protection against the lineage that's contained in FluMIst, but not any protection against challenge with a strain that's in the opposite Influenza B lineage. So that's what you would expect.

Then we also looked at the immune response in young children, 6 to 36 months of age, who are vaccinated either with FluMist or with an activated vaccine. And they got two doses of vaccine. And we looked at their serum antibody responses following

vaccination, after their one dose or two doses, and if you look at the HAI response in these children, you can see a very nice vigorous antibody response, as measured by HAI to the B-lineage contained in the vaccine.

And also if you look at drift strains within that lineage, you see a good antibody response that is highly actually than what you see with an activated vaccine in that age group.

If you then test those same sera using a microneutralization assay, you can then see a vigorous immune response to the B-lineage contained in the vaccine, a good response to the drift strains, but absolutely no microneutralizing antibody detectable to the vaccine, to the non-vaccine lineage.

So I think those data all would agree with what Dr. Couch told us earlier.

And then finally we, Dr. Couch presented the head-to-head study that we just completed, the Belshe publication, and showed

that you couldn't draw any conclusions based on the wide confidence intervals between the two vaccine strains. And as Dr. Couch mentioned, the way that study was analyzed was that the not well mapped strains consisted of a bucket of strains containing Yamagata, drift strains, and also the non-vaccine lineage of the Victoria strains.

So there is no way you can sort that out looking at those data, the immune response to the vaccine lineage or the non-vaccine lineage.

I looked also back at some previous years in which vaccine efficacy studies had been done with FluMist, when fortuitously the circulating strain was of the opposite lineage as contained in the vaccine. And again, all those studies were analyzed in the same way where the non-matched strains consisted not only of the opposite lineage, but also of drift strains within the vaccine lineage. So, it was very difficult to make

any conclusion based on these data that we have any reason to think that you would achieve cross-lineage protection from FluMist anymore than you would from an inactivated vaccine in this age group.

Thank you.

DR. KARRON: Thank you. At this point if there are no other people who would like to make a comment during the open public hearing, we'll move to Committee discussion. And what I'd like to do is put up the slides that Dr. Weir had up at the beginning with some of the discussion points.

Okay. While he's actually putting those slides up, I have a question of my own. I think maybe they're for Dr. Cox or Dr. Couch, just something of interest to me, which is this has to do with drift among Influenza B strains. And I was wondering within the B/Victoria lineage or within the B/Yamagata lineage, how much drift do we see over the years as compared with A-strains?

DR. COX: Oh, okay. Antigenic drift is slower just like the genetic changes are slower in B than in A. And we don't really know the reasons why, but it's, I would say roughly half to a third of the rate, genetically, and antigenically, probably about the same.

DR. KARRON: So just I guess to sort of understand, when we have switched back and forth over the years between Yamagata lineage and Victoria lineage, with each switch are the viruses very different? You know, a Victoria that we chose lineage virus that say we chose this year as opposed to two, or three, or four years ago? I'm just trying to get a sense of that.

DR. COX: It probably, you know, I would have to go back and really look at it analytically, but if there's a significant time interval then there would be a difference. If not, then you know, if it's only, for example, we've seen in the Yamagata

lineage we've seen B/Florida, which was one of our reference strains-like viruses for a number of years. And we don't see a change really from those B/Florida-like strains in the Yamagata lineage.

And like -- right, but when we hadn't had circulation of the B/Victoria strains for a period of time, then we had a big change between the previous B/Victoria strain that had been in the vaccine prior to that, resurgence of the Victoria.

DR. KARRON: Thank you. Dr. Farley?

DR. FARLEY: Well, I had a follow-up to that and a couple of other questions. But in looking at the, it was slide number 3 on our handout from Dr. Gagneten. It almost looked like, which was kind of showing the percentage of Yamagata versus Victoria in one year, and what the vaccine was, and then what happened the next year. We, for the last four or five years, we've been in the pattern of

going two years with one and it's almost, if you looked at that, if you had just alternated years rather than done two years in a row for each one of them, it seems like we would've been closer to the mark. And I wondered, I mean if we went back and kind of re-analyzed it, would there have been something near the end of the previous season, the season that was a good match, the last things that were isolated, would that predict the reversal that you'd see the following year.

And I just wondered if one of the other options to discuss was just that automatically we assumed we were going to alternate years and can we come up with a system where it would give us an early option, in terms of the strain, so that could be the first thing they work on the next year, whether the off season or at the very beginning of the following season.

So that's one of my questions. And I guess the other is much more

hypothetical. But it seems like with this kind of stable 2 lineages that it's a perfect candidate for molecularly constructed antigen, where you would put the key parts of both of those together. And it seems to me that, again, the idea of trying to modernize the process that this, the Bs, would be the first good candidates for trying to work on that option, that approach, and get it incorporated into our thought process. I mean I know that will take years to go through the regulatory issues, but it seems like this one would be a good one to put in the two stable antigens.

DR. EICKHOFF: Well, actually my comment sort of takes off from what Monica just said because of the several options that Bob Couch spelled out. The one that I found most intriguing was simply to alternate between the two lineages year-to-year, pretty much irregardless of what one expected to be predominant that year. And that was the one option that Mr. Colgate had no comment on, did

not consider it, and so I wonder if Mr. Colgate might comment about that option in particular.

DR. COLGATE: That would cause us absolutely no problems at all.

DR. KARRON: Actually as a follow-up question to that, would there be a potential advantage in terms of, an actual advantage in terms of vaccine production? That is to say if you could make the Influenza B strain every year at risk because you would know it's either going to be Yamagata --

DR. COUCH: Every year you would know one strain you could start with in B-strains.

DR. COLGATE: If you could tell us that, we'd be very, very happy, yes.

DR. KARRON: But just because then you would never be in a situation of potentially not having, you know, if there were going to be say, as we talked about this morning, the H3N2 change --

DR. WEIR: I was going to say --

DR. KARRON: Anyway, yes?

DR. WEIR: -- and I think Nancy is too, you still have to pick the right strain.

DR. KARRON: Right.

DR. WEIR: Okay.

DR. KARRON: Right. And Nancy, yes?

DR. COX: I think that it's also important when you're thinking about, when you're thinking about the big picture you have to know not only what proportion of Yamagata and Victoria lineage strains are circulating in the U.S., but what proportion they made up of the entire influenza activity that was ongoing. And that's, you know, in some years it can be a big problem if you have a mismatch. In another year, if you have relatively little B-activity and very few outbreaks, if you have a mismatch, it really doesn't have the clinical impact.

And so I think that looking at it

simply, you know, in this dichotomous way over-emphasizes the problem that we sometimes face when we have a mismatch. Sometimes it really isn't that important clinically because we have very little B-activity.

The other thing is that if the U.S. decides to do this, would decide to alternate, I just want to emphasize we would have to choose the right strain. There wouldn't be an automatic okay, go ahead with the old, whatever it was before, Victoria lineage or Yamagata strain. But also, the U.S. could be out of sync with the WHO recommendations very easily. So that would be a potential disadvantage for the manufacturers that Tony didn't bring up.

So, and what sometimes happens is that globally you'll see one picture where a certain lineage will predominate, whereas, in a particular country or particular region of the world you'll see another picture. And that was very true because Victoria viruses,

I'm sure you covered this while I was out of the room, but Victoria viruses continued to circulate in China, specifically in Southern China, co-circulate with the Yamagata lineage viruses. Well, they caused very little activity, if any, elsewhere, anywhere else in the world.

DR. KARRON: Right. And I assume that it was issue like that that led to the recommendations that Bob talked about, which is use whatever is appropriate in your region.

DR. COX: Exactly.

DR. KARRON: So in those sort of years you would not be out of sync because I assume that everyone was manufacturing differently and according to the needs of the region.

I wonder actually if this kind of issue has every been discussed at WHO or ever come there as an issue, this issue of a problem with B.

DR. COX: It has not been

presented in this formal way, where pros and cons of the different alternatives were really spelled out and discussed. So this is a really good way to look at the problem.

I had one question for FDA. If a tetravalent vaccine, including two B-strains and two A-strains were to be licensed, would you have to go through the same regulatory process if you were to have three A-strains, that is two H3s and 1 H1, and a B-strain. Or would the fact that you have 60 micrograms or whatever number of micrograms would be decided be, and you looked at that quantity of antigen and found it to be safe, and effective, and not to be interference. Would that be sufficient data for you to be able to generalize and say you could have two H3s, instead of two Bs if, for example, the B/Victoria lineage did circulate only in China, as it did in the past for a period of time?

DR. WEIR: Okay, I think I got it.

So you're saying if we license the quadravalent with, in this case, two As and two Bs, then could we switch and As and Bs in any sort of combination in the future without --

DR. COX: Yes, yes. So that say we were facing a year like this year where the As --

DR. WEIR: So, in other words, two H3s the next year if that became?

DR. FARLEY: And just to add a little complexity, more complexity, could H5 be one of the antigens?

DR. WEIR: Okay. So we haven't thought about this that much. I think that, I'll just speak off the cuff and then let Norman correct me. I think that the simple example, if you really had four and you licensed it and it was safe and effective, probably strain changes would probably be pretty easy to manage. Now, I haven't thought about the H5 possibility.

DR. BAYLOR: And I think that adds to the complexity because an H, unless you take it even further, an H5 we're gaining experience on H5. So in the near future, H5 may not cause as many problems, but you could take it out to an H7, an H9, and there where we may not have had a lot of experience, I think it would be much more complicated.

DR. WEIR: Yes, I guess the other scenario is a little simpler because we would at least be assuming the 15 micrograms is effective as well, whereas if we don't know that with the H5. But as Sara pointed out, I mean we are talking about clinical data to support the, you know, not only the safety but the efficacy, you know, to make sure no interference from one strain to another, the addition.

DR. KARRON: Dr. Self and then we'll take a comment from the audience.

DR. SELF: I'd like to go back to this point about the antigenic variability

within and between lineages. I mean my read of this data and some of the comments was that most of that variability is between lineages. And the slow rate of evolution would sort of support that idea. If that's true and variation within lineage is fairly slow over time, then the selection earlier of a strain within a lineage would be much easier. And that would have some important implications about manufacturing.

However, Nancy, you indicated and I was getting, you know, vigorous head bobbing across the way that selection of strain within lineage would still be a very important. Where, which is it? Would selection of strain within lineage be able to be done reliably sooner if lineage was set?

DR. COX: That's a very, very difficult question to answer. If we were looking at switching to the Yamagata lineage, we have strains that we've had basically, one strain we've had in our back pocket for a

number of years. So given the fact that we are very actively pursuing egg isolates and characterizing them more vigorously than we have in the past, I would say that on balance, because the B-viruses do tend to evolve more slowly, it would be easier but it wouldn't be guaranteed that we could come up with that earlier selection. But it would certainly be a lot easier than trying to do that for the H3s.

DR. SELF: So then the strategy of alternating years, which I find sort of theoretically fascinating, but I'm not sure is the best solution, or maybe a quadravalent but would split those. I was impressed at how similar the data looked for the seven and a half would make that total B-component able to, manufacturers to start that process at considerably less risk earlier. Is that fair?

DR. COX: I do, I think that's fair with the caveat that those data were derived from immunization of young, healthy

adults.

DR. SELF: So one of the down sides, one of the cons listed by Dr. Couch in the option with the quadravalent half dose was the lack of data --

DR. COUCH: The half dose data was healthy adults. And I'm told, this is hearsay, but there is a large study done by the military of basically the same thing, but it was all much larger numbers, all healthy adults and found the same thing.

And the data we want are the two on each end, preferably the children. But we don't have that data.

DR. SELF: But lack of data in the cons distinguishes from all the other cons in that you can remedy that. Most of the other cons you can't do that. You just have to live with that.

DR. COUCH: I want to ask just for my information and maybe help a couple of questions of Tony. If you took the scenario

of I don't care seven and a half or fifteen, you can comment on the two, but two of them, see, and let's take the seven and a half I like best, you only have to make half as much but you have to make two of them, what does that do to the time frame? You know, do you have to close down and a long time to start up again and use the rest of your eggs and so forth?

DR. COLGATE: Not really because we're changing between the H1, the H3, and the B anyway, especially at the end when we're trying to balance the strains. So it's really a matter of having a reference strain early and being able to get the reagents so that we can formulate. So it is really, again, things which are, to some extent, out of our hands. As I was trying to explain before, we have to work in cooperation with everyone else. So if we have the strains early enough and the reagents are there, then it's just more hassle basically is putting four strains together in

a season.

DR. COUCH: And then if you went for a full 15, could you then slide that back instead of starting in December, why, we give you one of the, I mean in January we give you one of the antigens and you start in December?

DR. COLGATE: That's a possibility. But as I said before, some, the problem is that some manufacturers in Europe are producing for the Southern Hemisphere as well. So their production, and also H5 production goes in that time. I guess the only answer really to 15 micrograms of each is to increase capacity. And I mean that can be done with sufficient notice, basically, and investment. I mean all these things can be done if it's done in a controlled, planned way.

DR. COUCH: No question about hassle, but some of them are a little easier and doable than some of the other options that we talked about.

And my last question, I'm not sure whether it's for you or for FDA is I don't know, and maybe somebody else does, where do we stand with regard to development of cell culture vaccines in the pipeline and that sort of thing? Can comments be made on that because everybody is waiting for that other option to come into the considerations for flu vaccines.

DR. COLGATE: I don't know.

MR. TSAI: I'm Ted Tsai. I'm an employee of Novartis Vaccines. Novartis has an MBCK cell culture vaccine that for which an application has been submitted to the EU and for which we have some plans for the U.S., including a manufacturing plant that's been, for which construction is already underway in Holly Springs, North Carolina. So there is a cell culture vaccine based upon MBCK cell production that is emerging very soon.

DR. COUCH: You may not be able to say it, but you've got to have some sort of

time line. Is that three years from now, five years from now, or can't you say?

MR. TSAI: We can't predict what the EU regulatory authority will say.

DR. COUCH: Well, assuming they're cooperative.

MR. TSAI: Well, they have the application. And as I said, we have plans to submit an application to the U.S. And there are other manufacturers with cell culture vaccines in the work as well for the U.S.

DR. KARRON: There is someone who has been waiting very patiently in the audience.

MS. CAVANAUGH: Nancy Cavanaugh, MedImmune. I just had a clarifying comment, I guess, about the quadravalent vaccine, and in particular the regulatory and clinical pathways that were described by Dr. Gagneten, and whether those would be similar for the live attenuated vaccines. Those were specifically described for the inactivated

vaccines.

DR. GAGNETEN: Those, I'm sorry. Those ones would hold for licensed products. So it would hold for MedImmune also.

MS. CAVANAUGH: Thank you. And actually before you sit down, could I just ask in terms of as we're talking about this half dose, seven and a half microgram, obviously you don't measure your doses in micrograms, but does that have relevance when you're considering FluMist or is that then just a quadravalent vaccine and it almost doesn't matter whether it's ten, 7.5, or it's half that, which is not much. I mean how would you interpret that?

DR. KARRON: Right now we're considering both options. You know, the same dose for four vaccine strains or yes, half of each.

MS. CAVANAUGH: Okay. Thank you.

DR. KARRON: Dr. McInnes?

DR. MCINNES: I'd like to push the

envelope on the amount of antigen that can be manufactured as opposed to reducing the dose that we're delivering. And I say that because I don't think we have ever optimized the amount of antigen we've delivered, to optimize for immunogenicity and deficacy. And even though we did see very similar responses in the study that was for healthy young adults. So I'm a little reluctant to just assume that, you know, moving towards a half dose, half strength concentration on each of the Bs is the solution.

So in trying to push again about the amount of antigen that could be manufactured to produce, at a minimum of 60 microgram per unit delivery, however that be divided up, I'd like to ask about the life of the manufacturing facility. I've only ever visited during the day. Does it work round the clock? Is it possible to push the amount of time that can be in a 24-hour period? I mean do you work all night?

DR. COLGATE: Basically, it really depends on your manufacturing. But the limiting factor is the number of eggs that you can incubate basically. So it's the number of eggs that you can handle in a working day. And that working day, I guess, could be 24-hours.

But really, the simplest way would be just to increase the size of your facility to buy 25 percent, I guess, and operate that way, rather than try to hot-bed everything. I mean if you try, if you stress the facility too much by running it 24-hours a day, it's going to crash. And there have been examples of that.

DR. MCINNES: Talking about the same period working 24-hours a day. No, I'm serious.

DR. COLGATE: No, the facility as well. I mean you basically, you have to allow time for cleaning and preparation and make sure everything is done in an orderly way. If

you try to compress too much in, eventually you fall over. It's really better to do it in an orderly way and just increase your capacity for processing eggs to the amount that is needed to go out at the end of the day.

DR. MCINNES: Tony, I'm sorry, so I'm pushing you here. So I'm hearing that in fact we work a traditional daylight time. There may be some cleaning and campaigning going, but you're not loading eggs in, in what could constitute the other half of the clock, right? There's not a night stock that works the same kind of work as the day stock?

DR. COLGATE: We have an evening staff who actually do the cleaning in preparation for the rest of the day.

DR. MCINNES: Okay.

DR. COLGATE: And certainly in the downstream processing, we are actually working a 24-hour shift.

DR. COUCH: Am I correct that basically what you're saying, Tony, is we're

going to increase dosage, you know, and I'm interested in antigens besides B, you have to have increased facility capabilities? Is that what you're saying?

DR. COLGATE: That's it basically. Do it properly or you get no vaccine in the U.S. one year.

DR. KARRON: Dr. Jackson?

DR. JACKSON: Just regarding the half dose. I mean I guess, I think we do know some things. We know in the elderly the response to the 15 microgram is diminished and that there is clearly a very strong dose response, you know, in Dr. Kyle's studies and others. If we give more antigen, we get a better response. And we think more is better in that regard. And then when we go down to the other end of the age spectrum, particularly infants, you know, Dr. Englund's studies and other work that's been done indicate that the response, in particular, to B after a single dose of vaccine is very poor.

And even after two doses, in some cases, doesn't seem to be great.

We also know that in a good year only about half of children who are supposed to get two doses actually get two doses. So I'd be very concerned about cutting the amount of antigen in half in those two groups for fear of what might happen assuming of what we know what a correlation there might be between antigen, antibody level and true protection.

DR. KARRON: Dr. Farley?

DR. FARLEY: This is a question for the manufacturers. I'm wondering, from a practical standpoint, given this discussion, and if we were to choose to go down the route of quadravalent vaccine with say this 60 microgram total, so not making the compromise on the antigen content, what would be the time table of when this could even possibly happen? I mean are we talking about two years down the road, or more, or less?

DR. COLGATE: That's a difficult

one really. I mean it normally takes two to three years to get a new plant up and running. Increasing capacity by 25 percent would really depend on the individual circumstances of the company. If they have space just to increase the size of the facility, then I guess it could, may be done earlier.

But I think also the regulatory hurdles are probably going to be the constraining issues basically. And I think we, I think we need some kind of clear directive about that. That is, is it required and there is a regulatory pathway and what kind of clinical requirements are also there. I think it would need to be spelled out to us very clearly exactly what is required and the mechanism for doing it. And if that's done, I'm sure, as we have done in the past, we would respond.

DR. KARRON: Dr. Wharton?

MS. BAXTER: Marguerite Baxter with Novartis Vaccines. I just wanted to add

to Tony's comment to sensitize the Committee. The other factor that would have to be considered is it would actually be necessary to enact tax legislation to include a quadravalent vaccine in the vaccine injury compensation program. Because the way the law is written now, it only covers trivalent influenza vaccine. So that would also need to be a step in the process that would need to be factored in.

DR. WHARTON: Yes, it seems like given that this is likely to be a somewhat long range process that is being really the follow-up from the last couple of annual VRBPAC meetings on influenza strain selection with some in-depth discussion this afternoon would be for FDA to, you know, to be able to define for us, or to be able to define what the regulatory pathway is that such products would have to go through. And I'm sure there are some clinical studies that would need to be done so that we all would be sure we

understood what a quadravalent vaccine would mean.

And so given that we are on a journey here, I think. I think we're not planning on getting there this afternoon that those are some steps forward that would move this process forward, just as this discussion has as well.

DR. STAPLETON: Yes, I think just as several people have eluded to, it would be interesting and should be feasible to retrospectively look at drift within different B-lineages and come up with some confidence intervals with how likely you are to have a major mismatch, based on previous years, which might actually improve the at-risk manufacturing process.

DR. COUCH: I just wanted to add that I tried dose-response data to Influenza B in infants and very young children. I couldn't find anything. None.

DR. KARRON: One other question I

have and I don't know if this would be useful or not, but we're also, we're in a changing era with regard to influenza vaccination. We're vaccinating more children than we ever did before and we're increasing the age range in which we vaccinate children. And I guess I was also wondering as part of this journey, if you will, whether it's useful to do any kind of modeling to look at the various options, taking into account the B-lineage strains that have circulated, the rates of vaccination, if you alternated strains in a vaccine what would it do? If you had a quadravalent vaccine, let's say of 60 micrograms, what would it do? We may not know enough about half doses to really be able to model that, but whether it would be useful to do some of that as part of the thinking process.

Are there other comments, thoughts form members of the Committee, or FDA, or from the audience?

Yes, Dr. Eickhoff?

DR. EICKHOFF: As part of this process, could we formally ask CBER and/or CDC representatives to take the issue of alternating strains year-to-year to WHO for their consideration next year?

DR. KARRON: I don't know --

DR. COUCH: Well, since you're at the hand, this is almost to the side, sorry. But I almost did it up there but I forgot. I wanted to, I think we've done it before, let's thank CDC, and Nancy, and Dr. Klimov, and Dr. Ye for that presentation this morning because that's a huge amount of work that they bring to these decisions for us. And one of my reactions was that if they'd just give us less data, they'd probably have much less discussion, and the decisions we'd make would be much simpler, but we wouldn't encourage that.

DR. KARRON: Absolutely. Of course, I think we should thank all of the

people who've worked very hard on our behalf.

I do though want to follow-up on Dr. Eickhoff's question and ask whether these deliberations could be brought back to the WHO?

DR. COX: Yes, I think it would be very important to bring these deliberations back to WHO. We do often spend extra time; we even started our meeting on Sunday afternoon this past year so we could spend half a day deliberating about H5 vaccines and going over that data. So we do find time for special topics and I think it would be very useful to invite, and we can invite outside experts. And it would be very useful to have the same kind of deliberations and really get feedback, because on that one occasion or two occasions, as Dr. Couch pointed out, we did have to say within the WHO recommendations, either B/Vic or B/Yamagata lineage virus, whichever is most appropriate, because the distributions were very different.

I think that it would be extremely useful to begin thinking about clinical trials. And exactly what it would take to put together a clinical trial that involved 15 micrograms of each B, and seven and a half of each B, that would really help answer some of the questions that have come up today and give us a lot more substance to deal with as we move forward with some of the difficult decisions.

DR. KARRON: Norman?

DR. BAYLOR: I just wanted to say, I mean, what we'll do as far as the FDA, I mean we look forward to working with the manufacturers and probably pursuing this discussion a little further. We have meetings with the Influenza Manufacturing Group Pharma, and this is something I think we can bring up as an agenda item and discuss the feasibility of this. And what we can do internally is we can do some, create some scenarios on what kind of clinical trials we would need or

develop to answer some of these questions, you know, using, you know, with all the options, looking of the options of alternating, or a quadravalent, what would it take. We can actually outline what we think would be a likely clinical trial to design.

I think also, Ruth, your comment about the modeling I think would be important because I really, I think we need to know among the options what do we really gain. I mean it would really be helpful to say if we go this route we gain this much. And that way we'll have a better idea of which one of the options to pick, or do we pick any of them. I mean, as Bob had indicated in his first option, do you stay the course. And I think it's important to evaluate all of those.

DR. COUCH: My last slide which I didn't use said data is needed.

DR. KARRON: Any other comments?

In that case, I'd like to thank everybody for attending this VRBPAC meeting

and we're adjourned.

(Whereupon, the above-entitled matter went off the record at 3:30 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript

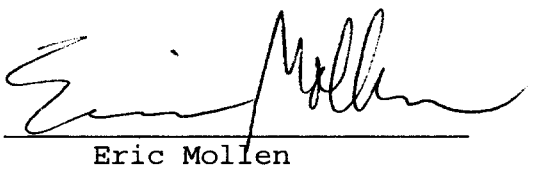
in the matter of: Vaccines and Related Biological Products Advisory Committee

Before: Food and Drug Administration

Date: February 28, 2007

Place: Gaithersburg, Maryland

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



Eric Mollen