efficacious.

But there are some very important considerations to keep in mind. In principle, if you want to produce a recombinant hemagglutinin, you do not need to grow or handle a live virus. You can use a well-defined cell line versus an undefined egg production. There's also an enormous search capacity, because these products can be produced in a mammalian or monoclonal antibody production facilities.

And if you think about it, the worldwide production capacity for mammalian cell culture is about 2.5 million liters. And if then imagine that you could produce 1 million doses of 135 micrograms of vaccine per 10,000 liter in a 5-day production cycle, you could imagine that it is feasible to produce billions of doses in matters of weeks.

It's also important to point out that the antigen that you make using a

recombinant baculovirus approach is an exact match to the H5N1 that is naturally appearing, so you do not need to make a reverse genetics modified strain. I also want to point out, as was pointed out by Dr. Couch before, that a potential influenza pandemic doesn't focus around age 5 alone. If we look at the last about 10 years, there have been many different avian viruses circulating with various impacts on humans. And this slide, the only purpose of this slide is that there's not just H5 but there's also H9 and H7, and as has been pointed out, H2 might been present a greater threat.

So what we have done at Protein Sciences is we have produced four additional hemagglutinins. They have been cloned from strains with pandemic potential, and they were produced using the general hemagglutinin purification process that we also use in the development of our inter-

pandemic vaccine. I believe strongly that a recombinant protein-based influenza vaccine is the most vital, proactive approach in fighting against a potential influenza pandemic. As was indicated earlier, it will take time for antibodies to develop, and if you can prime the immune system, that can have a major advantage.

We plan to produce and market a prophylactic pandemic vaccine after FluBlok has been approved. It is clear that you need a large safety database before you can develop such a vaccine, and therefore we have been and are conducting quite a number of clinical trials, and I want to very quickly highlight those trials.

We are conducting at this very moment a trial in young children age 6 months to 59 months. We expect results in the second quarter. We are also conducting an immunogenicity but also efficacy study in elderly or people 65 years and older. The

immunogenicity results of this study are expected in the second quarter. And a couple of months later, we will also have efficacy results. We earlier found I a field study that the commercial dose that we selected, and it's important to point out that this commercial dose will contain three times the antigen content of the regular influenza vaccine, so it will contain 45 microgram of each of the hemagglutinins, was 100 percent effective against cell culture confirmed influenza in subjects that presented with influenza-like illness. CDC defined influenza-like illness, even against drifted strains. We characterized all the strains, all the viruses from this study, and they all represented drifted strains.

As far as effectiveness goes, there was a 54 percent reduction in subjects that presented with CDC-ILI versus placebo. So we demonstrated in this study that a hemagglutinin-only vaccine can be

efficacious and effective without neuraminidase, and we also showed that the vaccine was highly immunogenic. More antigen leads to better immune responses as has been demonstrated or written in the literature for quite a while. We were able to show protective antibody levels for all antigens for at least 6 months.

We also earlier in collaboration with NAIAD conducted a study in the elderly where we particularly defined our endpoints against around the H3 antigen. These studies were published by Treanor et al in 2006. And as you can see here, there is a clear dose response effect. When given more hemagglutinin, you will get a greater sera conversion.

We also were asked by the Journal to perform a subset analysis because, as we know, as you grow older, your immune system may become more senescent, and therefore the right part of this graph is also quite

interesting. And if you keep I mind that we selected the purple dose as our commercial dose, that gives you some reference.

Now the baculovirus technology provides speed, cost and safety. It also provides a rapid response to emerging strains. So in other words, if tomorrow a new virus is identified and we know what antigen could convert protection, we would be very rapidly able to develop a vaccine.

There is not need to handle a live virus. And if you keep in mind that the latest outbreaks around SARS all came from laboratory or places where they were working with viruses, you can imagine that this is a risk that you cannot underestimate. As I mentioned before, we use the same antigen that is actually circulating.

Our next steps are that we are going to further evaluate the two clinical studies that are currently ongoing. We will

initiate an efficacy study in the 2007-2008 season in a very large group. We expect to initiate our BLA filing in the fourth quarter of this year. And subsequent to that, we will initiate the development of a prophylaxis vaccine.

And in case it wasn't clear, I am an employee of Protein Sciences, so that will be my conflict of interest. Thank you.

DR. KARRON: Is there anyone else who would like to speak during the open public hearing?

(No response.)

DR. KARRON: Seeing noone, we will take a break until 3:30 when we will reconvene for a discussion.

(Whereupon, off the record at 3:17 p.m. and back on the record at 3:41 pm.)

DR. KARRON: Okay. I think we're going to go ahead and begin if people in the back of the room would please take their

seats, it would be very much appreciated. And I think the best way to begin this discussion is to really go through each of the slides, each of the items that Dr. Toerner put up for our consideration. So we'll begin with this first one which has to do with the issue of assessment of immune responses, both the kinds of assays used and assessing responses following prime and following boost. So at this point, I'd like to open those issues for discussion. Comments?

I think maybe what we can do is start with one of the last items first and then perhaps move up, which has to do with the use of HI antibody assays versus microneutralization assays as a measurement of immune response. Would anyone like to comment on that?

DR. COX: Thanks. I think that there's a growing body of evidence that indicates that HI assays using horse red

blood cells are really good assays for detecting antibody to H5. But in our experience at CDC, and I can just speak to that and to some experience elsewhere that I've heard about, the microneutralization assay, although it's a lot more labor-intensive is still the gold standard, and there are some unusual effects that you can sometimes see with horse red blood cells depending on the animal and the test and the antigen and so on. So I think that it's really fantastic that we have now the ability to screen using the horse red blood assay, but I think the microneutralization test actually is better in reliably detecting antibody to H5.

DR. KARRON: So would you perhaps advocate using both tests as measurements of immunogenicity?

DR. COX: I think that at this point in time, it would be a good idea to use both assays, and as more and more data

are developed, perhaps it would be possible to move to the horse red blood cell assay because it is so much easier. But right now I think we're still at a stage where we need to do more assays and more comparisons and really get the cutoffs right.

DR. KARRON: Dr. Toerner, I was actually wondering if you could elaborate a little bit on your first two points there, immune response assays following prime and boost and what you wanted to elicit from the committee, comments you wanted to elicit on those points?

DR. TOERNER: The point that I wanted to make is regarding the first bullet point, the immune response assay following a prime. What I would be interested to hear is the heterologous immune response following a prime, would that be supportive evidence of demonstration of appropriate priming across protection in contrast to following subjects over time and

administering a heterologous antigen to the subjects and then measuring the immune response to the subjects following a boost administered a future time point. Does that --

DR. KARRON: So if I'm understanding this correctly, I wonder if maybe Dr. Treanor has data that could bear on this point at all, and that is to say from your original studies where you immunized with Hong Kong/97, did you then go back and look at those -- before those individuals were boosted, did you ever test their sera and look antibody responses to 2005? Is that the kind of thing that you're asking?

DR. TOERNER: Yes, that's correct.

DR. TREANOR: That would be a really good idea but we didn't do that. It's another thing on the list of things that would be good to do. The sera are

available but they haven't been tested.

DR. KARRON: Dr. Self?

DR. SELF: I don't know too much about this system, but I can compare the nature of this discussion to what we've had in HIV vaccines. And there are very well-standardized, broad panels of reagents, of pseudo variants in this case, and a system of labs and assays that have been highly standardized, validated, proficiency panel tested so that endpoints taken at standard times from the last boost can be compared across, you know, many different studies with, you know, some reliability. I'm not hearing anything of such a system here. Maybe there is something like that but if there is, exercising that kind of a system and having those sorts of reagents and standardized assays sounds like it would be a very good thing.

DR. COX: I think that you're absolutely right and there's a lot of

thought going into that type of system so that you have standard sera. And I think that the NIH is involved in some trials that will produce some standard sera. And also having a standardized panels of antigens that could be used to test so that you can actually compare from study-to-study. And I would certainly advocate for a lot more harmonization among the studies that are being conducted so that we can -- and a lot more head-to-head comparisons so that we can really understand what is going on in terms of cross-protection, how much greater cross-protection you get with adjuvants using a specific antigen, and a whole variety of other things. So these panels are -- discussions are occurring about how to get these panels put together correctly.

DR. SELF: So in HIV, these panels are also tiered that begin with the homologous virus and then sort of expand, not going to the next tier unless you see a

good breadth in magnitude in the current tier. And the assays also span both antibody as well as cellular immune response. I heard earlier that there's some interest in the role of cellular response here, and so maybe there's also something --

DR. COX: Yes. There's not a lot done but John may want to speak to more studies that will be done to look at the --

DR. TREANOR: Well, in the study that I presented, a large proportion of the subjects had peripheral blood mononuclear cells obtained. The laboratory that's going to be assaying those has really spent quite a bit of time validating their cellular assays and showing reproducibility and reproducibility of thawing cells and all that kind of stuff. And I think they're just beginning now to start actually doing the assays on the PBMC that will provide another way of looking at immune responses beyond antibody.

DR. SELF: So the reagents there, the antigens there to reflect, you know, variability in the targeted virus population raises a whole another series of problems, so that's another issue to -- that you'll have to address at some point.

DR. KARRON: Dr. Eickhoff?

DR. EICKHOFF: John, correct me if I'm wrong, but I thought one of the things that I heard you had on your list of things to do, which must be very long by this time, was to take the sera from the Sanofi vaccine that we just looked at this morning that you'd carried out and to test those sera against clade 2 and perhaps clade 3 viruses, is that correct, as a measure of heterologous response?

DR. TREANOR: Yes. I think that, you know, it would be fascinating to know what kind of response revaccination generates against the original antigenic exposure and it would be a very great

practical interest to know whether these individuals are also responding to clade 2. And so, you know, this is a assay development sort of issue, but those will be done at some point by the reference lab.

DR. EICKHOFF: Well, for that reason, I think heterologous or testing against heterologous antigen would be very useful as outlined in that slide, simply because it may provide some -- it may correlate with a level of boost that you get with a heterologous virus or will it correlate with the level of boost following boosting with a heterologous virus.

DR. KARRON: Dr. Couch?

DR. COUCH: Well, just a couple of comments for the discussion. One was that John made essentially and that is what we're talking about when we're looking at antibody and boosting antibody, that's an operational definition of prime and boost. If you really want to know whether a

person's primed or not, you're looking at whether those lymphocytes are recognizing that antigen or not, and we've got th technology to do that. See, I was unaware until he told me a little earlier that Jim Crowe had been trying to do that specifically for H5. If that's really a goal of pre-pandemic vaccinations, then the priming assay should be out there being looked at right now and know the differences in dose and age and maybe underlying disease in terms of what the variables are that determine priming, because that will define your response at a future time. And that's a far better and more accurate way to define priming than the way we're talking about it with operational definitions prime and boost.

Second is that there are a lot of different ways to do neutralization tests. When we use the term microneutralization, we're usually talking about the test that

was described originally by Maurie Harmon that Jackie Katz has picked up using at CDC, and I think that the British version is essentially the same thing. And even the way we do it, which is somewhat different -- essentially all of them -- they don't have to be that way, but essentially all of them are another way of measuring antihemagglutinin and antibody, so I think it's important that you keep that in mind. Because if they don't correlate, well, then you've got to raise a question as to exactly what your neutralization assay is measuring and antihemagglutinin and antibody is the antibody we've all been focused on as the desirable immune response, not the only one that might be useful but the desirable one and the one that we're still using as a standard for making decisions on influenza and influenza vaccines.

So the major value of neutralization, we've been doing a version

of it for four years. In our hands, it has greater sensitivity than the HI test. I didn't make that comment earlier this morning, but it's perhaps useful for the way some of the thinking that's got on here that the HI test is really a fairly crude and relatively insensitive test for antibody. So you need to think about that when we talk about how we're going to try to use it.

DR. KARRON: I think that probably we should -- I think we may be able to move on to the next slide. I think if I can summarize what I think I'm hearing for the consensus -- I think the consensus is you probably want to measure heterologous protection both at the time of prime and at the time of boost using modern technology as well as using -- as just using at conventional antibody responses. Okay. Yes? Sorry.

DR. GELLIN: A question really for Bob. You got into it a little bit, but

we're talking mostly about hemagglutinin, and I guess the question is given that the neuraminidase may be less variable, how do we use this as an opportunity to get a better understanding of what neuraminidase immunity buys us?

DR. COUCH: I'm sorry Rob Webster's gone, but you might say that we fall into two camps, the neuraminidase proponents and the neuraminidase is not so significant. I'm on the first camp that neuraminidase antibody is a highly desirable antibody. And what we know about the neuraminidase for at least the H1 and H3 -- that's Nancy's territory -- is it's less variable than the hemagglutinin. And of course, Ed Kilbourne's not here now but that would be his basis for proposing very strongly that the neuraminidase does need to be evaluated and is -- I mean this is H5N1, see, we're talking about and in H1N1 is an N1 neuraminidase, you see.

Maybe I better make a question out of it to Nancy then. Do we have the data to say that there is no cross relationship between those and that the N1 that we're currently vaccinating with on an annual basis would have no benefit for H5N1 as we know that neuraminidase. I don't know any of these questions and/or answers.

DR. COX: Unfortunately, we don't have the answer to these questions. I think there was a recent publication out of Rob's group which indicated in an animal model there was some cross-protection and there -- I think it remains to be seen. Of course, we know that because of the ages of a number of the individuals who have died of H5N1, they surely were exposed to H1N1 viruses in their lifetimes and that certainly didn't protect them. So I think the jury is still out and we have a lot more to learn about the role of neuraminidase.

DR. KARRON: John?

DR. COUCH: I might say that's a separate comment from the fact that neuraminidase is a useful antigen and immune responses to neuraminidase does indeed convey protection.

DR. TREANOR: I was just going to add that in that study that Rich Webby did, we did send sera, and there is a low level of recognition of the avian N1 in a panel of human sera from people who had received conventional vaccine, so the levels of neuraminidase-inhibiting activity are substantially lower against the avian N1 than they are against the human N1, but there is recognition of the avian N1 by human sera.

DR. COUCH: I suppose you might say then they are primed.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: I'd like to ask a question of the flu people. Also like Steven, I'm from a different background.

But does the prime boost suggest that there are T-cell epitopes that are linked to the B-cell epitopes, and if so, have those been mapped at all? And if not, that would seem to be something that should be done.

DR. KARRON: There has been substantial sequence analysis of those viruses, and I know that a number of epitopes have been potentially identified. The Hong Kong and Vietnam viruses are actually about, I think it's, 90 to 95 percent similar on an amino acid level. The differences are all in the antibody epitopes and more or less. So there probably would be potential cross-recognition, I would think anyway.

DR. KARRON: Okay. I think we'll move on to the second discussion point which was to discuss the feasibility of long-term clinical studies of prime and boost, whether studies should be six months, a year, greater than a year and also this issue of

collaboration among different sponsors. And I think the intent there was if one sponsor might have had a clade 1 virus and another had a clade 2 virus, how might that occur. Yes, Dr. Robinson?

DR. ROBINSON: I just want to acquaint you with some contracts that we let out in January for antigen-sparing of pandemic influenza vaccines. One of the characteristics of those three contracts is that the contractors who are known publicly as GSK, Novartis and Iomai will submit to HHS their adjuvants for evaluation with the same antigen or other antigens for human influenza to inform public health decision makers as to if there can be a mix and matching that, during an imminent pandemic, if those adjuvants would work with antigens that we have in our stockpiles, because most of the stockpile is in a bulk form. So we are encouraging that and we're in the planning stages right now with the

manufacturers of the adjuvants and also the antigens.

And so what we're looking for now is guidance from CEBR to help us come up with the proper study designs that would be acceptable and also the regulatory pathways as we move forward to that so that we can present a suitable case to VRBPAC in the future years.

DR. KARRON: Other comments? Yes?

DR. FARLEY: This is a little bit off the main focus of this discussion right now, but one of the things that I noticed about the modeling is that -- and what I think I'm aware of with Longini's as well -- is that the focus on prioritization to children seems to be sort of important and kind of drives, in some ways, these models of getting it out there early and having it work well, and I wondered if there needs to be any modification of the route with which

this phase of development -- I mean should we be working more on or increasing the emphasis on pediatric trials and understanding their role in the prime and boost and whether they're going to tolerate the adjuvants and those sorts of things?

DR. KARRON: Jesse?

DR. GOODMAN: Well, I think that's a good question. You know, we have encouraged pediatric trials of pandemic vaccines, but we've done that cognizant of sort of the special status of children in how we ought to have some safety data to support that before such studies are done. But yes, you notice even with the nonadjuvanted Sanofi vaccine, there is a small pediatric study that's been done. And then I think this is an important point -- and then I know that others who are developing new vaccine, once they have substantive evidence of safety and immunogenicity in adults are planning

pediatric studies, and we're encouraging them.

Now I would say the -- you know, maybe Dr. Couch or others might want to comment -- but I think the notion of children as sort of hyper spreaders and important -- both important to protect in a pandemic and also potentially important in transmission, I think that the first one everybody would agree. The latter one, I know it's not as well documented as it could be, but I think that we should get that data. You know? But I don't think I'd want to go prematurely with novel compounds into children.

DR. KARRON: Dr. McInnes?

DR. McINNES: I want to follow-up on Robin's introduction there. We have not taken a position that an adjuvant can be thought of as a stand-alone project. I mean there's no adjuvant licensed. It's a product that has antigen in combination with

an adjuvant that comes forward for licensure. So I'm trying to -- maybe you could explain a little bit what the plans are for the product characterization of these, what essentially are, off the shelf mix and matches and the characterization of the product, the pre-clinical safety evaluation of that product given that you might be looking at varying concentrations of either component and then what you're thinking about in terms of the Phase I? I mean you would have a characterization piece, a pre-clinical safety piece, an immunogenicity piece and moving to human studies.

So if you look at that sort of, you know, could really be a 20 by 20 box or a 10 by 10 box or a 50 by 50 box. I mean I have no idea what the plethora of combinations could be. So could you tell us a little bit about that strategy and who's going to take this one and how is that going

to work when you don't have manufacturers necessarily envisioning a commercial project here?

DR. ROBINSON: Well, I'll leave it to the manufacturers whether or not they consider their products with adjuvants to be commercially viable or not on that count. But essentially, we do recognize exactly what you just said is that adjuvants are not stand-alone products in our world. What we would like to know is if it is possible to actually develop formulations of vaccines that actually can be filled into antigen concentrations that can be tested in pre-clinical animal models, preferably in a fair challenged model with the adjuvant either pre-formulated with it or admixed prior to giving the vaccine to the animals and then challenging them.

From that data, two things will pop out. One is that we may see that some formulations, some antigens, the way that

they are actually formulated as a bulk product and then finally into a final container product, are contraindicated for other adjuvants. That's a possibility we would find that out so that we can strike that one out.

If they are compatible and they do afford in animals a reasonable, and in these cases both homologous and heterologous cross-protection, then the data supported in the toxicity studies also, then we would envision a subset of those going into Phase I clinical studies for safety, immunogenicity, and cross-protection as far as cross-reactivity for serological samples. So that in a nutshell would be what we think.

But you're exactly right. I mean one of the things that we do want to understand is is there compatibility of these different products, and we would understand that in the pre-clinical setting

to move forward.

The desire for this, the reason for this is that if we have stockpiles of bulk antigen that are there and then we can increase the amount of doses that we can actually put into people's arms, then it behooves us to at least look at, in pre-clinical studies, you know, are these compatible and then, as I said earlier, what can the CEBR give us as a pathway to move these forward and presumably to use these under emergency uses authorization. I don't foresee these mixing and matching of antigen and adjuvants as a licensed product except for the homologous systems where the company has developed and has moved forward with the licensure of a particular antigen with that adjuvant.

DR. KARRON: Dr. Toerner?

DR. TOERNER: Just to provide some additional clarification with the bullet point of the collaboration among

different sponsors, I think what our goal was to emphasize the value of following subjects wh o were enrolled in studies. If you go back a few slides or look at your handout, the cohort A and cohort B were those study subjects who've received one dose or two doses of vaccine. We think there's value in following those subjects over time in order to administer a different vaccine or a different clade, so that's the point that we wanted to make about the collaboration among different sponsors.

DR. KARRON: Essentially, to be able to replicate studies like Dr. Treanor's over time?

DR. TOERNER: Yes. For example, if a sponsor is pursuing development of a vaccine for use during a pandemic and they have those data, they have those immune response data from study subjects in cohort 1 and cohort 2, that there perhaps could be a mechanism to follow the study subjects out

in order then to demonstrate the possibility of priming.

DR. KARRON: Dr. Goodman?

DR. GOODMAN: One thing we'd appreciate input on -- it may just be that this is very straightforward, but if we can go back to Dr. Toerner's slide about heterologous prime and boost, you know, are these basic outlines of, you know, the 1 or 2 doses then followed by a boosting dose at 6 or 12 months, you know, do people looking at those think that they're reasonable approaches or have other suggestions? We all agree we should get as many useful assays and samples at the different time points to understand whether we can predict a good boosting effect, etcetera, what heterologous immunity might have existed before the boost, etcetera.

But, you know, the real question is does this kind of approach where you'd get, for example, one, or I suppose this

doesn't have two followed by boost, but one or two doses? And, you know, there are many, many variables and approaches to doing this, but, you know, for example, a six-month boost might be comparable to being immunized in a sort of pre-pandemic-emerging pandemic followed by a new vaccine. A year or greater might be similar to just a population being pre-immunized. Are these sort of reasonable approaches.

And the other issue I heard raised to both Dr. Treanor, and I think is a very -- again, you can't do everything at once. You have to start with the simple stuff and get your principles, but this issue of might these approaches -- there might be different approaches to dosing. You know? And then I know you're not going to be able to anser it, because we couldn't even answer it this morning for a much simpler question. But what should be thinking about in terms of what is a

meaningful heterologous response?

So I want to frame first of all is this a reasonable structure, because manufacturers are, as you heard, may be starting to do or even doing some of these studies, and we can encourage, as I said, that is if these are just additional arms to ongoing studies, we could get data a year or two before you might do it if you did these studies just sequentially. So we do want input is this the right track.

And then as Joe said, it would be wise to look at not just with one manufacturer's vaccine against another's but in the real world, in an emergency, the boosting could occur with -- you know, you're not going to be able to say did you get manufacturer x and now we're going to just give x. So I hope that's helpful in terms of framing some of our questions.

DR. KARRON: Dr. McInnes?

DR. McINNES: In some senses,

this takes me back, to the haemophilus influenzae days of thinking about -- and it's back to this operational issue of priming and boosting and, in fact, whether you are really testing boosting with a full concentration or whether you should be really looking at -- do you need one dose to prime or do you need more than one dose to prime I think is one question. And then the boosting piece, in fact, I'm not sure of that with 45 micrograms you're actually testing boosting. You may actually need to go with a much lower dose concentration to evaluate boosting.

But I think you have -- we have to be very careful what the question really is on the table. And there are so many questions that could be asked here. So you could -- I mean theoretically, you could take group A and wonder why -- you could look at waning immunity with time and look at what they look like boosting them at --

you know, giving a second dose at 15 months. It just sort of never ends. So I mean I think what you've put up on the table is as reasonable as -- for a starting point. And I think maybe it's better to actually raise the principles around which you want the studies to go rather than trying to define specifically timing.

DR. KARRON: Dr. Couch?

DR. COUCH: Yes. You made me -- probably like a lot of them, I didn't think about it when you were saying it, so you made us start thinking about it. And if you really focus on, as you said, pre-pandemic use, I guess there are a whole lot of variables that you'd like included in these studies and then they might well become prohibitive. This is not bad. If I added one besides that, I would add Vietnam at each of those boosting sites as comparison to that heterotypic boost, the homotypic boost. That would be the scientific data

I'd like to see.

DR. KARRON: I'd actually just like to -- not that I can begin to answer this question -- but the issue of what kind of a heterologous would be considered adequate? I have no idea but I would say that just sort of to echo something that Dr. Couch said, I think one of the other reasons to use more modern methods to look at priming besides the fact that it actually looks at what is we think of when we biologically of what priming is is that it may, in fact, be much more sensitive, that you might be able to detect responses that you cannot detect using conventional antibody assays. And so I think that should be kept in mind.

DR. COUCH: Part of what that homotypic would give you that I wanted to put in there was the question of whether you would need then still another boost of Indonesia because you'd have the Vietnam.

DR. McINNES: And then depending on when you're going to do your serology, I"m not sure the timing on whether you will really be able to characterize the kinetics of the response. Maybe it is a very early response, and I think we have to bear in mind that you may have to actually be pulling blood much more frequently maybe as an initial study to characterize the kinetics.

DR. KARRON: Dr. Cox?

DR. COX: Yes. Given a lot of the discussions recently about the need for developing countries to also have access to H5 vaccines, I think the looking at what the quantity of antigen that it really takes to prime and to boost is incredibly important, and so you've got to have some dosing components in there, because we really do want to be able to conserve antigen as much as possible.

DR. KARRON: Dr. Treanor?

DR. TREANOR: Well, I was just going to say two things. Just bear in mind that all the experience that we have with H5 that relates to this sort of prime boost idea involves a two-dose schedule for the priming. So we don't have any information about a single dose of one thing followed by a dose of another. And the pediatric data suggests, as I understand it, that that's not quite as good when there's a strain change. So that's the thing.

And the other thing I would say is that I think -- bear in mind that the assays for neutralizing and hemagglutination-inhibiting antibody which we're using now have been the subject of quite a bit of effort to standardize. And even so, it's well-recognized while within a lab, they can be very reproducible, the absolute titers that two different laboratories on the same sera are not always in complete agreement. I would think that

you would be faced with similar or perhaps more challenging issues trying to really standardize and validate the types of flow cytometry and gamma interferon ELISPOT assays you might be using to look at some of these other cellular responses. And I think that will be a major challenge for looking at some of these other questions related to priming and boosting.

DR. KARRON: Dr. Goodman?

DR. GOODMAN: Something somewhat encouraging -- it doesn't shed light on this but is that certainly both in the literature and that for those of us who were at the WHO meeting, we did hear several vaccine developers of some of the newer vaccines show, you know, heterologous immunity without boost, so there may be some background there to work with. And also, on Nancy's point about antigen content, of course, you just heard a presentation suggesting that potentially with certain

adjuvants, that may greatly reduce the antigen content.

But, you know, we're going to be stuck with the challenge of trying to answer some of these questions without the studies becoming, you know, impossible or overly complex. And, you know, I see this sort of 12-month framework that's up there, and maybe with the additional of the homologous control, you know, as a good one, I think if we were to having to use high amounts of antigen, then the idea may be at some of these boost points, you know, titering what you boost.

But we're not going to be able to answer all these questions at once. And as I said, I also think there are companies, for example, doing studies or thinking about studies that may inform -- you know, again, just like we said this morning, in three months we could have additional data from one place or another, but we do appreciate

these suggestions.

I didn't hear a comment on, you know, what -- you know, should we just be happy if there is heterologous immunity? Do people have comments on tying that as was suggested in the discussion of how the Europeans are looking at it to efficacy in the ferret? What do people think of those issues? Because we will at some point bring back to you probably one of these, hopefully, wildly successful vaccines and say does this evidence for priming or heterologous protection, you know, merit either a claim or an indication.

DR. KARRON: Nancy?

DR. COX: I did notice the sort of question implicit in the presentation about the use of animal models, and I do think that it is informative to use the ferret model. It's perhaps the best model that we have right now, best defined for H5. There are some clear endpoints that can be

obtained using challenges and so I think that it would be very useful to include the ferret model for looking at cross-protective antibody.

DR. KARRON: Okay. I think we should probably go on to the last question -- discussion point I should say. And this has to do with -- actually, one more -- Christine, sorry. This has to do with issues related to safety considerations, pre-licensure safety database, and the issues related to novel manufacturing processes or adjuvants.

One comment that I would make that, really, Dr. Robinson's comments made me think about with the sort of mix and match issues is I think that raises real -- there are efficacy considerations. There are also safety considerations, because every adjuvant behaves differently with regard to inducing immune responses when combined with different antigens. It also

may have different safety profiles when combined with different antigens. And so I think that's something that has to be considered. Dr. McInnes?

DR. McINNES: I'll put something out. So in a pre-pandemic setting, I see a relatively high bar to demonstrate safety, a requirement for safety, and I would see that in needing to be in many thousands of people. And I don't know how many thousands. One would have to sort of give that some consideration. But I certainly don't see it on the same scale of what we talked about this morning. So I think this is really no different than the way we would think about licensure of other vaccines, that when you're going to be introducing into a broad population, we have a responsibility to be documenting and characterizing the safety profile. And maybe this gets done in a staged way, in a stacked fashion, but I think that we are

looking at large studies.

DR. KARRON: Comments, reactions? I'll say that I actually agree with Dr. McInnes in terms of pre-pandemic and pandemic use and that, you know, my sense is the bar would be very different in terms of safety profile in those two settings. Dr. Wharton?

DR. McINNES: Yes. I would agree with your comments and in the sub-bullet, there were serious adverse events, those at a frequency of 1 per 100,000 not likely to be detected in a typical pre-licensure database, I think we're unlikely to be able to detect those in atypical pre-licensure database either. It's hard to imagine a study large enough to do that, so I think that one is left with having to come up with plans where those can be identified in the post licensure setting.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: One issue thought

of as you were talking actually, Ruth, and as with an adjuvanted vaccine down the pike when it's coming up for review, since there can be differences in reactivity and immunologic response to different antigens, it will be important, I think, as different clades come out, even though those are fairly subtle changes structurally, that even clade to clade evaluation will be different, and it's not going to probably be like our current system I would think but I'm not sure as far as being able to go one year to the next. And I guess I'd be interested in what the influenza experts on the other side of the table and the top table if they agree that's going to be an issue or not.

So the question is do you think with an adjuvanted vaccine, because you can have quite different responses based on formulations with different antigens, that the year to year variability will need to be

assessed more diligently than the current system with the non-adjuvant vaccine?

DR. COUCH: Well, I think you can only comment on that in a general way, and I don't want you to -- you're looking at me, but you're not looking at an expert on this subject. Let me say that.

But adjuvants, if they do what we want them to do, increase the immune response, and the greater the immune response the greater the cross-reactivity if there's something like an antigenic drift that we're talking about -- so I think the general concept we would all accept -- now when you start talking about an individual antigens -- adjuvants, there are TH1 adjuvants and there are TH2 adjuvants and their immune response is different, I'm sure the cross-reactivity would differ. And that's data that we don't yet have for a lot of antigens including just a little bit of

data, I'd say, on influenza.

But in general, I would say that if an adjuvant does what we want it to do and expect it to do, it should increase the cross-reactivity if that's what you were driving at, Jack.

DR. STAPLETON: Not exactly.

DR. COUCH: Not exactly? Try me again.

DR. STAPLETON: No. I just was curious from a regulatory standpoint, safety standpoint if that's going to require a different level of diligence and study annually on a year-to-year basis. And I throw this out as a rhetorical question.

DR. COUCH: Oh, safety questions are a whole new subject. When you bring up safety questions for adjuvant and most people know the experience with incomplete Freund's adjuvant in the 1950's. You know, there were probably 10 to 100,000 vaccinated, and the responses, they were

reported in the military primarily, in the use of this vaccine were excellent. A lot of it was used civilian wise as well, and the adjuvant was shown very clearly to be dose sparing. The general figure I carry in my mind from that data is you could get the same antibody response with about 25 percent as much antigen if you used incomplete Freund's adjuvant along with your vaccine. And that was considered highly desirable in 1957.

But if it hadn't been shown inappropriately to produce polyoma tumors in mice, and which it was an artifact in retrospect and hadn't been shown to produce sterile abscesses, although they were very rare, it might still be around today as an adjuvant that we knew a great deal about and could be considered quite useful. But that's not where we are. So I think that really you're asking for an FDA comment, but I'm not sure to a considerable extent

adjuvants need to be evaluated, that we're almost starting over again with relation to flu vaccine despite the fact that there was a good bit of experience in the 50's.

DR. KARRON: So I think what Jack is asking, probably of the FDA, is if you were to license an adjuvanted vaccine for a particular pandemic strain, then would the laws of sort of strain change apply? Or given that you have an adjuvant, would you need to reassess in the context of that, say, a new clade? Do I have that correct?

DR. STAPLETON: You said that better than I did. Thank you.

DR. BAYLOR: I think -- and let me make sure I have the question right -- you're saying if you have an adjuvanted antigen and then we change the strain the next year, then would we require additional data for that? And I think, you know, the manufacturing process is going to drive this. The first product, we're going to

look extensively at that adjuvant and the safety of that adjuvant with the antigen. We would have to really think about whether adding a different antigen would really change sort of the profile of that. And, you know, in the absence of data, I can't say that.

But sort of on the normal under just general principles, you would not think that that would be the case, that changing that antigen would elicit some kind of safety issue that you didn't pick up in the previous. But -- well, we don't know that. And so we would have to think about that really seriously, to think about whether that new antigen would add some higher concern. But again, it's sort of in the once you've approved the adjuvanted whatever that is that year, it almost falls into the strain change paradigm. But again, it's -- we're dealing with the unknown.

DR. KARRON: Dr. Hetherington,

did you have a comment before?

DR. HETHERINGTON: No. I think it's been answered.

DR. KARRON: Dr. Treanor?

DR. TREANOR: This is a more theoretical -- just a hypothetical issue that's brought up by something that Robin mentioned and this may be naive, but as I understand it, there's an issue with the possibility that we would have difficulty supplying the number of doses we need for a pandemic vaccine even if all the manufacturers who are capable of making the vaccine were operating at full strength. And in this process of evaluation of adjuvants, we might go through, you know, five, ten different adjuvants and find out that a particular adjuvant, adjuvant x, is absolutely ideal for a pandemic vaccine.

So the question would be under what circumstances can now manufacturers a to z use adjuvant x for their pandemic

vaccine so that we would have an adequate supply? And this is where the mixing-matching idea comes from. And I don't know what the pathway for it is for should a very, very important adjuvant be discovered but only be made by one company, how would this be able to be used by other manufacturers to improve the supply?

DR. KARRON: Jesse?

DR. GOODMAN: Yes. I think that is what Robin was trying to address. I think there's a whole number of issues which are both scientific and then intellectual property-business relationships, etcetera. But I think the scientific one, and this is I think what triggered Jack's question and what Robin was commenting on, is we have a lot -- there probably are more concerns about an antigen made with one manufacturing process and an antigen made with another manufacturing process and whether when those are mixed with ideal adjuvant x in

potentially different circumstances or time points, that could raise a bunch of issues about formulation, stability, immunogenicity, safety.

So I think there would be scientific issues that would need to be addressed, you know, probably through clinical studies. And how you would address those would be different perhaps in an emergency versus for a routine product. I think what Robin was saying is that at least in HHS's contracting, they've tried to preserve some ability to at least do some of the studies that would answer those questions.

But, you know, I think what we would hope is that as data emerges, if there are ideal candidates, they'd become -- you know, or if some -- I mean there may be more than one candidate that works very well and more than one approach, and there's always value to having that. But if there aren't,

then I think this would sort of be both the national public health issue as to how you brought the best technology to bear and, to some degree, a business issue.

But I think the big question here and we heard several knowledgeable people comment at WHO that it -- you know, there are things about the chemistry of the manufacturing process and we're aware of these, too, but may not always line themselves to this being a simple matter of, you know, taking x and throwing y in it and add simple things like pH, polarity, water content, etcetera. All these kinds of things may affect behavior with an adjuvant. So -- but this is another area where we need more science.

DR. KARRON: Dr. McInnes?

DR. McINNES: I'd like to ask the card-carrying influenza accolades for some input on -- I was recalling the data from VTEU studies where there was a very clear

dose response curve, immunogenicity wise dose response cure, and then thinking -- and I don't recall the slide as clearly -- but I was struck with the GSK immunogenicity of really a very pretty much flat immunogenicity response and not much of a dose response curve based on this is the adjuvanted product, that they really pretty much looked the same across the spectrum of those concentrations of antigen. And is that typical for -- who has recollections of adjuvanted flu vaccines and whether you have a dose response curve or whether you get almost an all or none, there's some critical level that it -- you get as an equivalent immune response?

DR. TREANOR: Pam, that's more or less identical to the pattern that's seen with MF-59 as well.

DR. COUCH: The same with MF-59 with H9, too, with the adjuvant, but the dose responses there are for non-adjuvant.

DR. STAPLETON: Yes. Have you done studies where you've actually reduced the antigen down to levels where you can say that you don't have a dose response? It's maybe that you just get such a good response in that slide, 3.8 micrograms, maybe they just need to go down to .038 micrograms?

DR. TREANOR: I haven't actually done these studies directly, so I don't know what the whole dose range is that's been studied.

DR. COUCH: I think -- well, you want to -- we'd like to see the lower anchor for dose responses. That's part of what you're saying. We didn't see that one there. But one of the more important aspects -- or maybe one of the important aspects of those, what look like, comparable responses to lower doses is the duration of that response and the pattern of that response which out to be dissected. And I'm probably sure GSK is doing that.

DR. KARRON: Dr. Innis, would you like to make a comment?

DR. INNIS: I would about the dose response. What we've seen is that there is a very slight dose response. I didn't show you the GMT's and so that distorts things a little bit, but there is a slight dose response. But I expect that we're way up on the shoulder of need or maximum response. And the operation -- of course, we would like to test much lower hemagglutinin concentrations. The issue is that the SRID assay is qualified down to formulate as low as about 2.5 micrograms. And so if we wanted to do less, we could, but we need to come up with ways to do dilutions that everyone would have confidence in.

And an even larger question is if you found that these lower doses were, in fact, effective, potentially effective, let's say immunogenic, how would you

actually then be able to formulate commercial product and release it into the marketplace. So we're hamstrung right now by the limited quantitation of the SRID assay as it's specially formulated.

And this is a very, very serious issue. So if you have thoughts about that, we sure would like to hear about them.

DR. COUCH: My comment on the dose response is more of a scientific one than it is a manufacturing one, Bruce, but just scientifically, you'd like to know and understand what's going on with those responses in that adjuvant group, that's one. Manufacturing is quite different. Nobody questions your concern there.

The single radial immunodiffusion has problems, and it is an old but has been a reliable assay. But I'm not alone and you're not alone in saying that better and newer assays need to be developed for this purpose, for standardizing vaccines, and

pandemic flu may be part of the stimulus to be doing that. And I can't comment on -- for some of the people who are beginning to look at some of these things, too. So that concern about the radial diffusion assay, hopefully, is only a temporary one.

DR. KARRON: Yes. Would you like to make a comment?

DR. WILLIAMS: Yes. My name is Mike Williams. I worked in the flu lab at the FDA from 1976 to 1996, now a consultant to the pharmaceutical industry. I'd like to add in 1978, when SRID was instituted as the potency assay for flu vaccines after the extensive clinical studies, we could not release final vaccine at the potency level of 7.5 micrograms, and potency of vaccine was released on monovalent concentrates as it was really up until really recent years. So there is a mechanism to do this. I think the FDA needs to get creative in working with the manufacturers. I would say if you

can make a pandemic vaccine down in the .1 or less microgram range, then you really ought to be doing it, and there are mechanisms to do that and there is historical precedence to do it.

DR. KARRON: Thank you.

DR. WILLIAMS: Any questions?

DR. KARRON: Yes. Dr. Goodman?

DR. GOODMAN: I would just say we're certainly open to creative solutions to solve the problem. I also do think, you know, with modern chemistry and analytic tools, we can probably maybe do both, find ways to deal with the present situation and also probably find analytic methods that might improve on what exists, might even be better.

DR. KARRON: Any other comments that any committee members would like to make or members of the audience?

(No response.)

DR. KARRON: Okay. In that case,

I think our day on pandemic influenza is concluded. Tomorrow, we will begin again with discussions of seasonal influenza vaccine. Thank you all.

(Whereupon, at 4:40 p.m., the foregoing matter was concluded.)

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 27, 2007

Place: Gaithersburg, Maryland

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

Eric Mollen