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Center for Biological Products Advisory Committee

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P R O C E E D I N G S (8:30 a.m.)

Agenda Item: Call to Order and Opening Remarks/Introduction of Committee

DR. DAUM: Good morning. My name is Robert Daum. I'm a pediatrician at the University of Chicago, somehow in the role of chairing this committee. We welcome everybody to the meeting.

I'll turn the floor over to Don Jehn for some conflict-of-interest and other announcements.

MR. JEHN: Thanks, Dr. Daum. Good morning, everybody. As Dr. Daum indicated, I'm Don Jehn, the designated federal officer for today's meeting of Vaccines and Related Biologic Products Advisory Committee. I would like to welcome everybody to this, the 131st meeting of the advisory committee.

Today's and tomorrow's sessions are open to the public for the entire meeting. This meeting is described in the *Federal Register* notice of October 17, 2012. I would like to request that everyone please check their cellphones and pagers to make sure they are off or in the silent mode. Now I need to read into the public record the conflict-of-interest statement for the meeting.

The Food and Drug Administration, FDA, is convening the November 14 and 15, 2012 meeting of the Vaccines and Related Biologics Products Advisory Committee

under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all participants of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to the federal conflict-of-interest laws and regulations. The following information on the status of this advisory committee's compliance with federal ethics and conflict-of-interest laws, including but not limited to 18 USC 208, is being provided to the participants at this meeting and to the public.

FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict-of-interest laws. Under 18 USC 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts, when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussions at this meeting, members and consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including

those of their spouses or minor children and, for the purposes of 18 USC 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties, and also primary employment.

At today's meeting, for Topic 1, the committee will discuss and make recommendations on the safety and immunogenicity of an influenza A H5N1 virus monovalent vaccine manufactured by GlaxoSmithKline. This is a particular matter involving specific parties.

For Topic 2, the committee will discuss and make recommendations on the safety and efficacy of hepatitis B vaccine manufactured by Dynavax. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members and consultants, no waivers were issued under 18 USC 208.

Dr. Filip Dubovsky is serving as the industry rep, acting on behalf of all related industry. He is employed by MedImmune LLC. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with

their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by FDA for conflicts of interest.

The conflict-of-interest statement will be available for review at the registration table.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any of the affected firms, their products, and, if known, their direct competitors.

That concludes the conflict-of-interest statement. Dr. Daum, I turn the meeting back over to you.

DR. DAUM: Thank you very much.

We’ll now ask committee members to identify themselves and state where they are from and their area of expertise.

We’ll start, Dr. Dubovsky, with you. Welcome.

DR. DUBOVSKY: My name is Filip Dubovsky. I'm a pediatrician, ID specialist. I work for MedImmune, where I'm in charge of the clinical development for vaccines.

DR. DAUM: Thank you.

Dr. Eickhoff is not with us today. But there are no health issues. People will be relieved to hear that.

Dr. Levandowski.

DR. LEVANDOWSKI: I'm Roland Levandowski. I'm an independent infectious diseases and public health physician from Bethesda, Maryland. I'm here because I have a strong background with influenza vaccines.

DR. DAUM: I'll say.

DR. BENNINK: I'm Jack Bennink. I work at the National Institute of Allergy and Infectious Diseases. I'm in the Laboratory of Viral Diseases and I'm section chief of the Viral Immunology Section.

DR. PIEDRA: I'm Pedro Piedra, at Baylor College of Medicine, Houston, Texas. I'm a pediatric infectious disease specialist. I have interest in influenza and other respiratory viruses.

DR. MARCUSE: Ed Marcuse, University of Washington and Seattle Children's Hospital, pediatrician with a career-long interest in vaccines and immunization.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention. I'm in the National Center

for Immunization and Respiratory Diseases, where our national immunization program resides.

DR. MCINNES: Pamela McInnes, National Institutes of Health.

DR. BRADY: Nathaniel Brady, independent practitioner in allergy immunology, Colorado Springs, and I'm serving as consumer representative.

DR. GELLIN: I'm Bruce Gellin. I direct the National Vaccine Program Office at Health and Human Services.

DR. CHEUNG: My name is Ambrose Cheung. I'm from the Geisel School of Medicine at Dartmouth. My interest is in molecular pathogenesis of infectious diseases.

DR. HUDGENS: I'm Michael Hudgens, from the Department of Biostatistics at the University of North Carolina.

DR. AIR: I'm Gillian Air, from the University of Oklahoma Health Sciences Center. I'm a biochemist who works in influenza.

DR. TACKET: I'm Carol Tacket, from the University of Maryland Center for Vaccine Development. I'm an internist, and my expertise is primarily in Phase I vaccine development.

DR. GRAY: My name is Greg Gray. I'm a professor at the University of Florida and a public health physician.

I study respiratory virus epidemiology.

DR. WEIR: Jerry Weir, Division of Viral Products, Office of Vaccines Research and Review at CBER.

DR. GRUBER: Marion Gruber, Office of Vaccines.

DR. JAMES: Andrea James, infectious disease specialist, medical officer, Office of Vaccines.

DR. DAUM: Thank you very much. As I mentioned before, I'm Robert Daum, from University of Chicago, pediatric infectious disease, a bacterial person. I work mostly on staph and staph infections.

That concludes our introductions. We'll swing right into the topic of the day. Our first speaker this morning is Dr. Goodman, who I haven't seen for quite a while. Welcome, Dr. Goodman. He will introduce the topic to us.

Agenda Item: Topic 1: Safety and Immunogenicity of an Influenza A (H5N1) Virus Monovalent Vaccine Manufactured by GlaxoSmithKline

Introduction

DR. GOODMAN: First, I would like to thank CBER and the Office of Vaccines for inviting me to open this meeting today and also thank all of the advisory committee and the other participants and the public for their interest in this very important topic.

I'm just going to give a very quick bit of

background. You will hear much more about a number of these points as the day goes forward.

I think that the recent pandemic with H1N1 in 2009 provides a lot of illustrations of both the remaining needs in pandemic preparedness, particularly with respect to vaccines, and some of the potential of what can be accomplished. More recent global estimates have shown that even what appeared to be a relatively mild pandemic caused substantial morbidity and mortality. For example, one modeling study by Dawood and colleagues just published in *Lancet Infectious Disease* last month estimated about 300,000 deaths globally from this, quote, mild pandemic. Also of interest, it was the apparent burden of disease in many parts of the world that don't easily have access to high-quality medical and supportive care.

Within the United States, there were an estimated 61 million cases -- and I’m just sort of using midpoint estimates here; all of these are estimates with big confidence intervals around them -- 275,000 hospitalizations, and 12,500 deaths.

As we all saw, everybody worked together very hard to get vaccine out quickly. This was really a nice example of public, private, and intergovernmental and global cooperation. But despite that, there were a number of challenges in getting vaccine out quickly. Not much

vaccine was available to impact in the first wave. But despite that, it's estimated that something like 700,000 to 1.5 million cases of H1N1 were prevented, and several thousand hospitalizations and several hundred deaths. Obviously these numbers could be much higher if we could mobilize more vaccine more quickly.

Some of the factors contributing to a successful ability to intervene in a pandemic with vaccine include the kind of collaboration I talked about, which was truly an international effort. Those efforts continue. It's truly a public-private partnership, where everybody is working together in very real time, including to get the needed strains and reagents, manufacture of vaccines, and, where necessary, conduct studies.

In the 2009 pandemic, one of the things that enabled the response greatly was FDA's confidence, based on having a number of approved vaccines, to license monovalent pandemic vaccines as a strain change under established regulatory frameworks. This provided clarity to industry and others about pathways to quickly get vaccine out there.

In addition, I think, as everybody is aware of, there have been tremendous US Department of Health and Human Services investments in pre-pandemic preparedness that contributed, including manufacturing capacity and preparedness for a rapid public health response, including

stockpiling and distribution of vaccines and antivirals.

In many ways, I think we benefited from the 2009 pandemic, in revealing to us both strengths and weaknesses of the response system. But we know that the risk of pandemic influenza is going to stay with us and is serious. We still have no reliable scientific tools to predict what the next virus is that’s going to emerge, even though we have greatly improved surveillance. Things keep popping up and we wonder, will this become the next pandemic? We still don't know how to predict that.

One of the biggest concerns -- and, of course, what stimulated a lot of global efforts at preparedness -- was the emergence of H5N1 avian influenza, predominantly in Asia. Obviously, we are all relieved that in the many years since this virus first surfaced it has not become transmissible among humans. We are, of course, aware of experiments that show that it potentially could be. But there are many other serotypes that also remain a potential threat. I think everybody is familiar with the recent H3N2 swine-origin influenza. I think just as likely is that new virus types can emerge totally unpredicted, just like the H1N1 did in 2009.

Of course, the continuing circulation and cases of H5N1 provide opportunities to reassortment and mutation, which could enhance transmissibility.

What is the role of vaccines in responding to a vaccine? They protect individuals through immunizing them, but they also can have profound effects, if administered early enough, on transmission among the population. So they can be a very important intervention against pandemic influenza.

The bottom line just shows various pandemics of various severities. There's one error here in terms of the number of deaths from swine flu. I mentioned it's much higher than that.

What we're talking about today is a candidate adjuvanted vaccine against H5. As I said, H5 continues to perk along, primarily in Asia. This just lists cases reported through WHO, confirmed human cases. We have had several hundred. As everyone knows, what's very striking about this virus has been both its persistence and the mortality rate, in proven cases, of more than 50 percent.

Another challenge with this virus, as you will hear more about, is that it's generally poorly immunogenic, which really has led largely to investment in studies and efforts to make a more immunogenic H5 vaccine, for example, through novel adjuvants.

FDA has worked very interactively with our government partners and with the industry to try to move some of these vaccine candidates that could be more

immunogenic, and potentially more effective, forward. I think as this committee is well aware, there's currently one licensed H5 influenza vaccine, manufactured by Sanofi Pasteur, also as a result of good public-private partnership. This vaccine is non-adjuvanted and, reflecting the poor immunogenicity of the H5 hemagglutinin, has required two injections of 90 micrograms -- or, as most of you know, something like six times the normal antigenic dose.

It is included in the US national stockpile, but this very high antigen requirement for an H5 vaccine -- and even with that high antigen requirement, a somewhat suboptimal antibody response for non-adjuvanted vaccines -- has been a very significant impediment, both to having adequate stockpiles to deploy initially in a pandemic, and much more so, to rapidly produce sufficient vaccine for an effective response.

So there is a need for adjuvanted influenza vaccines with enhanced immunogenicity to improve both our stockpiling and surge capacity, again to allow reduced antigen use per dose. This has the potential to greatly speed production and availability of sufficient doses in a pandemic. This is not just a US issue. This is a global issue. Global supplies of hemagglutinin antigen and production of antigen are highly limited, despite

successful increases in vaccine capacity in recent years, both in the US and globally.

Non-adjuvanted vaccines have been very safe and effective and well proven, particularly in terms of their safety profile, which led to a lot of confidence in their use in the 2009 pandemic. But we all are aware that the efficacy of non-adjuvanted flu vaccines is not optimal.

Novel adjuvants may enhance both the degree of the immune response and also the breadth of immunity, the speed of the immune response, and provide additional benefits, which can be very important in a pandemic, where we know that viruses, just like in seasonal flu, may evolve or drift on a fairly substantial basis.

Today we're hearing about one of the candidate influenza vaccines with antigen-sparing potential that was invested in through the Department of Health and Human Services. We're going to be considering data to support both the safety and immunogenicity of the adjuvanted pandemic influenza vaccine called Q-Pan. This is a split-virion inactivated hemagglutinin-based vaccine. It uses a novel adjuvant, which the company calls AS03. It is manufactured by GlaxoSmithKline. For production of the basic underlying antigen, it uses the same manufacturing platform used for GSK's licensed seasonal non-adjuvanted inactivated flu vaccine, FluLaval.

This vaccine is intended to support pandemic preparedness and response, because, as noted, it has the potential to facilitate more rapid availability of a larger number of doses, as well as the more rapid onset of an immune response of enhanced breadth. If licensed, this vaccine will also be the first FDA-approved adjuvanted influenza vaccine available in the United States.

So we really appreciate your thoughtfulness and discussion of this application for this very important public health need. Thank you very much.

DR. DAUM: Thank you, Dr. Goodman.

We have a couple of minutes, before you leave the podium, if there are questions for your presentation. Dr. Levandowski.

DR. LEVANDOWSKI: I have more of a comment than a question. We talk about the responses to the H5 vaccines as being poorly immunogenic. I’m not sure we know what the word “poor” means in the context of H5, because we don't really have a true clinical correlation between any particular antibody level and a protective effect, either infection, illness, or death. I think it’s an emotionally charged word in some ways. I agree that we would like to see higher antibody titers, but we just don't know what the given antibody titers mean.

I think a further caution, with the information

that we have available from what has been published so far -- we need to remember that there are major differences not only between laboratories for testing the same sera against the same strain, but between different strains of H5 we're going to see different types of responses, based on the antibody assay itself, which is very straightforward. Hemagglutination inhibition and neutralization -- they are both very straightforward, but they give much different results in different laboratories and with subtle differences in the methods. For example, the horse red blood cells for H5 -- just different horses may give totally different responses for the same of sera. The red blood cells are not all equivalent.

When we say "poor," I think we mean lower than we would hope to see and that we believe that higher is better than lower. But I don't think we really know exactly what that means. So I would urge that we not use words like "poor" in describing any of the responses for any of the vaccines.

DR. GOODMAN: I think your points are all valid and well-taken. I would say that there is a big deficiency in our understanding of immunity to influenza. There's absolutely no question about that. I think what we can say is that the response to the H5 hemagglutinin seems very, very different than the response to other inactivated

hemagglutinins. There’s a much lower level of antibody produced.

What is interesting, for example, is that -- and, of course, that non-adjuvanted vaccine was approved because I think both the VRBPAC and FDA believe that it can offer protection. I think we’re on the same wavelength here. Yet there is something different about the immune response to this.

Also this is in the context of the fact that we know that even seasonal influenza vaccines that are non-adjuvanted have problems with their immunogenicity and do not reach the levels of protection against serious illness that we would like to see and that we expect with many other vaccines.

So I think it's a characteristic that we don't understand immunity to flu, given vaccines are not optimally immunogenic. And then there is something also different about H5. In fact, as you’ll remember, many people were very worried that 2009 H1N1 would be like H5, but we were very pleased to see that, no, it was much more like the seasonal immunogen.

DR. DAUM: We don't have all the data that we would like, but nevertheless they are what they are, and we just sort of plunge on and deal with them.

Any other questions for Dr. Goodman, comments?

(No response)

Dr. Goodman, we thank you very much. It's nice to see you and nice to hear you.

We're going to now turn to the main agenda of the morning. The presentation will consist of three parts. First there will be some background information, with some speakers from various branches of the government. Then we will have a sponsor presentation -- GSK in this case. Then we will have an FDA presentation as well. Then the committee will begin their deliberations.

To begin with the background presentation and the presentation of the questions, we have Dr. Collazo-Custodio. Welcome. We look forward to your comments.

Agenda Item: Background/Presentation of Questions

DR. COLLAZO-CUSTODIO: Good morning, everyone. Thank you, Dr. Daum, for your introduction, and Dr. Goodman, for your introductory remarks.

Today I'm going to tell you about influenza A H5N1 virus monovalent vaccine, adjuvanted, manufactured by GlaxoSmithKline. For my presentation, this vaccine is referred to as Q-Pan H5N1. This is not a trade name. You'll see why we refer to this vaccine as Q-Pan as I go through my presentation.

In terms of today's agenda, after I finish with

the background and introduction, Dr. Golding is going to give us an overview on vaccine adjuvants, particularly highlighting the mode of action for GSK's AS03 adjuvanted influenza virus monovalent vaccine. Dr. Robinson will then talk about the United States government programs and goals for antigen-sparing pandemic influenza vaccines. Dr. Bresee is going to offer the CDC perspective on pandemic vaccine effectiveness, highlighting the experience during the H1N1 pandemic.

We will then hear from GSK representatives. They are going to tell us about the product under consideration today. Then Dr. James is going to give us the FDA presentation of clinical data.

We will then convene to discuss and vote. I will present those questions to you.

In terms of the background, today I'm going to just give you a brief overview about currently licensed seasonal and pandemic influenza virus vaccines. Particularly I will describe the vaccine under discussion today, Q-Pan H5N1. I'm going to give you a brief summary of a discussion we had earlier this year regarding licensure of pandemic influenza vaccines, the demonstration of effectiveness. This is really to set the stage to discuss the pathway to licensure of Q-Pan H5N1. To conclude, I will present the questions to the committee.

In the United States there are several seasonal and pandemic influenza virus vaccines. For the purpose of today's discussion, I would like to highlight FluLaval, manufactured by GlaxoSmithKline. I'm also going to briefly mention Fluzone and an H5N1 influenza virus vaccine, both of which are manufactured by Sanofi Pasteur.

More than five years ago, as Dr. Goodman mentioned, we convened the advisory committee to discuss an H5N1 influenza virus vaccine. The vaccine is manufactured by Sanofi Pasteur using the same egg-based manufacturing process as the seasonal influenza virus vaccine Fluzone. The vaccine is included in the United States Strategic National Stockpile. The safety and immunogenicity data that was generated with this vaccine supported the dose of antigen and a dosing regimen.

During that discussion, the advisory committee recommended that the data supported the safety and the effectiveness of this vaccine for a particular use during a pandemic or in situations of high-risk exposure. Subsequently, the vaccine was approved in April 2007 for use in persons 18 to 64 years of age.

One key point here is that implicit in the approval of this vaccine was the acknowledgment that the effectiveness of the pandemic vaccine was inferred from Fluzone, the seasonal vaccine.

As we move on to the particulars of today's discussion, the portfolio of GlaxoSmithKline's egg-based influenza virus vaccines includes both seasonal and pandemic influenza virus vaccines. Their two seasonal influenza virus vaccines are licensed in the United States. They are unadjuvanted. They are FluLaval and Fluarix.

GSK's portfolio also includes pandemic influenza virus vaccines that are shown on the right-hand side of this slide. They are not licensed in the United States. They contain the AS03 adjuvant. They are Pumarix, Arepanrix, Prepandrix, and Pandemrix.

This slide also highlights the relationship between the pandemic influenza vaccines and the seasonal influenza vaccines in terms of manufacturing. As you can see, in red, Pumarix and Arepanrix are manufactured in Quebec, Canada according to the FluLaval manufacturing process, whereas Prepandrix and Pandemrix are manufactured in Dresden, Germany according to the Fluarix manufacturing process.

I would also like to highlight that the vaccine we're discussing today, Q-Pan H5N1, is authorized in the European Union as Pumarix. However, there's no post-marketing experience available with this vaccine.

There is post-marketing experience available with Arepanrix and Pandemrix. These vaccines were widely used

in the 2009 mass vaccination campaigns conducted during the H1N1 influenza virus pandemic. You are going to be hearing more about this post-marketing experience in today's presentations.

In regards to Q-Pan H5N1, you heard that the United States government contracted GlaxoSmithKline to develop and submit for licensure a candidate H5N1 influenza virus vaccine with antigen-sparing potential. The vaccine is to be included in the United States Strategic National Stockpile. GlaxoSmithKline submitted a biologics license application in February of this year.

The applicant is ID Biomedical Corporation of Quebec, doing business as GlaxoSmithKline Biologicals. As you heard, the vaccine consists of inactivated, split H5N1 influenza virus hemagglutinin antigen and AS03 oil-in-water emulsion adjuvant. The antigen is manufactured in Quebec, Canada according to the FluLaval manufacturing process. Hence, the vaccine, as I mentioned earlier, is referred to as Q-Pan or Q-Pan H5N1, for pandemic antigen manufactured in Quebec.

Each .5-mL vaccine dose contains 3.75 micrograms of hemagglutinin of the Indonesia strain, 5 micrograms of thimerosal as a preservative, and AS03 oil-in-water emulsion adjuvant, which consists of alpha-tocopherol, squalene, and polysorbate 80. You are going to be hearing

more about this adjuvant in Dr. Golding's presentation this morning.

The vaccine is supplied as two separate multidose vials, a vial of H5N1 antigen and AS03 adjuvant. These vials are combined prior to administration, yielding a multidose presentation of the vaccine that results in 10.5-mL doses. The vaccine is for intramuscular administration and is given as a two-dose schedule approximately 21 days apart.

The proposed indication for Q-Pan is for active immunization for the prevention of influenza disease in persons 18 years of age or older at increased risk of exposure to the influenza A virus/H5N1 subtype containing the vaccine.

Now I'm going to give you a brief summary of an advisory committee discussion we had in February this year. There was a lot that was said earlier this year. I'm going to try to capture that in two or three slides. I'll do my best to accomplish this.

One topic that was discussed in this advisory committee was in regard to the approaches for demonstrating the effectiveness of a pandemic influenza vaccine manufactured by the same process as a US-licensed seasonal influenza vaccine. This vaccine may have been licensed via two different regulatory pathways: the traditional

approval pathway or the accelerated approval regulations.

On the next slides I'm going to explain what these regulatory pathways are.

This scheme illustrates the pathway where the seasonal vaccine has been licensed via the traditional approval regulation. To obtain traditional approval, a manufacturer has to demonstrate the safety and the immunogenicity of this vaccine, as well as the efficacy of this vaccine, by conducting trials that show the efficacy of the vaccine in well-controlled studies.

To then license a prototype pandemic vaccine, the manufacturer must also accrue safety data, as well as generate immunogenicity information that supports the hemagglutinin dose, the adjuvant content, and the dosing regimen.

Doing this February discussion, the FDA proposed a pathway for showing the efficacy of this vaccine -- in this case, the effectiveness. The reason for this is because during the pre-pandemic period there is no circulating pandemic strain, so the conduct of the efficacy trials -- they are not feasible. So what FDA proposed was to infer the effectiveness of the pandemic vaccine from the efficacy of the seasonal vaccine. Via this approach, then the prototype pandemic vaccine is licensed via the traditional approval pathway.

Licensure of this prototype pandemic vaccine in the pre-pandemic period then allows for a strain-change supplement. Dr. Goodman referred to this regulatory mechanism. This then would allow the approval of a vaccine that's well matched to a circulating influenza strain in the event of a pandemic.

The other scenario is when the seasonal vaccine is licensed via the accelerated approval regulations. Accelerated approval may be granted for certain biological products for serious or life-threatening illnesses. In the case of a pandemic vaccine, approval would be based on the following:

• Safety data accrued with a prototype pandemic vaccine.

• Immunogenicity data. The regulations state that the approval is based on adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint reasonably likely to predict clinical benefit. In this case, we are talking about a hemagglutination inhibition antibody assay that's used to evaluate immune response.

• The regulations also state that approval is subject to the requirement that the applicant study the biological product further to verify and describe its clinical benefit. This is the conduct of a post-marketing

confirmatory study or studies.

This diagram here illustrates this regulatory pathway. As I mentioned, the licensed seasonal vaccine was approved via the accelerated approval regulations. This means that the efficacy of the vaccine has not yet been verified or demonstrated.

Then the manufacturer interested in licensing a prototype pandemic vaccine -- given the regulatory status of the seasonal vaccine, the vaccine would also be licensed via the accelerated approval regulations, meaning again the expectation that the manufacturer would conduct safety studies and generate immunogenicity data that support the dose and dosing regimen.

Here I would like to make a parenthesis to really draw your attention to this pathway, because it’s highly relevant for the discussion we’re having today on GSK’s Q-Pan H5N1 vaccine.

During the February VRBPAC we talked about approaches to demonstrate the effectiveness of this prototype pandemic vaccine during a pre-pandemic period. One option that was described, which is shown here, was that the effectiveness of this pandemic vaccine could be verified when the efficacy of the seasonal vaccine is confirmed.

Another pathway that was described was that the

effectiveness of the pandemic vaccine could be verified using observational effectiveness data with a non-US-licensed adjuvanted H1N1 vaccine.

Via either one of these options, the prototype pandemic vaccine could be licensed via the traditional approval pathway. Then again the same type of regulatory mechanism could be used -- that is, a strain-change supplement -- in the event of a pandemic to approve a vaccine that is well matched to the circulating strain.

During a pandemic, a manufacturer could also collect additional effectiveness and safety data for a pandemic vaccine. In fact, the applicant is expected to work with government agencies on plans to collect additional effectiveness and safety information when the pandemic vaccine is used. In terms of regulatory vocabulary, this is considered a post-marketing commitment and not a requirement under the accelerated approval regulations.

How does this apply to the pathway to licensure of Q-Pan H5N1?

As I have said many times today, Q-Pan H5N1 is manufactured by the same process as FluLaval, the unadjuvanted seasonal vaccine. Licensure of FluLaval, however, was based on a review of safety and immunogenicity data via the accelerated approval regulations. This means

that the efficacy of FluLaval in preventing influenza illness has not yet been demonstrated.

However, results from a controlled study to verify the clinical benefit of FluLaval were recently submitted to FDA by GSK. This is study QIV-006, the confirmatory study for traditional approval of FluLaval. You'll be hearing more about this study in GSK's presentation today.

Within the context of the regulatory status of FluLaval, GlaxoSmithKline submitted a biologics license application for Q-Pan H5N1 on February 22, 2012. The clinical package included safety and immunogenicity data accrued with the Q-Pan H5N1 vaccine in pivotal studies. It also included additional supportive safety and immunogenicity information, as well as effectiveness data from an observational study conducted during the 2009 influenza pandemic with Arepanrix. Arepanrix is GSK's AS03 adjuvanted H1N1 pandemic influenza vaccine manufactured by the same process as FluLaval. This really represents the option B that I mentioned in my previous diagram.

This observational study that was conducted during the pandemic offers important information about the effectiveness of the Arepanrix vaccine. However, after review, CBER does not consider the Arepanrix effectiveness study sufficient for traditional approval of Q-Pan H5N1,

due to certain limitations in the study. You are going to hear more about this in today's presentations as well.

Therefore, GSK proposes to confirm the clinical benefit of Q-Pan H5N1 using efficacy data generated with the seasonal influenza vaccine made according to the same manufacturing process. Again, what this represents is the option A that I illustrated for you in the previous diagram.

This diagram trying to represent a pathway to licensure of Q-Pan H5N1. Since FluLaval is licensed via the accelerated approval regulations and the efficacy data is under review, the prototype pandemic vaccine, Q-Pan H5N1, would also be licensed via the accelerated approval regulations, meaning that GSK will have collected safety information and also generated immunogenicity data that supports the dose and dosing regimen.

What GSK is proposing is that when efficacy of FluLaval is confirmed, the effectiveness of Q-Pan H5N1 is verified. In this approach both FluLaval and Q-Pan H5N1 will be approved via the traditional approval pathway in a pre-pandemic period.

I will remind you that this option was discussed at the February VRBPAC this year and the approach was agreed by CBER and GlaxoSmithKline also in previous regulatory meetings.

Once Q-Pan H5N1 is licensed, then we can have the same regulatory mechanism in a strain-change supplement to approve a vaccine that is matched to the circulating pandemic strain.

GSK has also committed to work with government agencies on plans to collect additional effectiveness and safety information when the Q-Pan H5N1 vaccine is used.

To summarize, the approach to grant traditional approval of the Q-Pan H5N1 vaccine is now option A. FDA has agreed to this option. It really is confirming the clinical benefit of Q-Pan H5N1 with data derived from the clinical endpoint efficacy study conducted with the seasonal influenza vaccine FluLaval. FDA views this option as scientifically supportable and consistent with previous regulatory actions.

During the review of the BLA, another approach was discussed. This one was not presented at the February VRBPAC. I just would like to mention it here to elaborate in the discussion we're going to have today. This approach would be for GSK to conduct an effectiveness study or studies during an H5N1 influenza virus pandemic to verify the clinical benefit of Q-Pan H5N1. Under the accelerated approval regulations, GSK would be required to carry out such studies with due diligence, and the studies would have to be adequate and well controlled.

Just to summarize what I told you this morning, the advisory committee meeting is being convened today to review and discuss presentations of safety and immunogenicity data derived from studies conducted with the Q-Pan H5N1 vaccine. The committee will be asked to vote on whether the available data are adequate to support the safety and immunogenicity of Q-Pan H5N1 for use in adults at increased risk of exposure or during a pandemic. The committee will be asked to discuss approaches to confirm the effectiveness of Q-Pan H5N1 for traditional approval.

Now I will present the questions to the committee:

1. Do the immunogenicity data support licensure of the Q-Pan H5N1 vaccine for use in adults at increased risk of exposure or during a pandemic? You will be asked to vote yes or no.

2. Do the safety data support licensure of the Q-Pan H5N1 vaccine for use in adults at increased risk of exposure or during a pandemic? You will be asked to vote yes or no.

Our discussion item is the following. Please discuss the following two approaches to confirm the effectiveness of Q-Pan H5N1 for traditional approval:

1. To confirm the clinical benefit of Q-Pan H5N1 with efficacy data generated with a US-licensed seasonal

influenza virus vaccine made according to the same manufacturing process.

2. To confirm the clinical benefit of Q-Pan H5N1 by conducting an effectiveness study or studies during an H5N1 influenza virus pandemic.

I thank you all for your attention. This, Dr. Daum, concludes my background presentation.

DR. DAUM: Thank you very much.

We're a few minutes behind, but if there are one or two clarifying questions for that presentation, this is the time. Dr. Wharton.

DR. WHARTON: If a pandemic vaccine has been approved under accelerated approval and the confirmatory studies have not yet been done, is it possible to license a matched strain as a strain change?

DR. COLLAZO-CUSTODIO: Yes.

DR. DAUM: Dr. Gellin.

DR. GELLIN: Is there a definition of clinical benefit?

DR. COLLAZO-CUSTODIO: I do have that in one -- can someone from FDA help me with that question in terms of a broad definition? Usually we mean prevention of influenza illness, but --

DR. DAUM: Dr. Gruber.

DR. GRUBER: We interpreted clinical benefit

under the accelerated approval regulations as being that a sponsor or an applicant would conduct clinical endpoint efficacy studies with the product. In other words, you would look for prevention of disease, influenza-type illness. You look at culture-confirmed influenza there as an endpoint. So it's different than basing the licensure on an immunogenicity endpoint, as we would do under the accelerated approval. Confirming the clinical benefit would mean a clinical endpoint efficacy study looking for prevention of disease.

DR. GELLIN: A specific nuance was whether or not priming -- however that might be defined -- could fall under clinical benefit.

DR. GRUBER: Priming? We have not had these discussions. The question is really if this would be -- you’re asking if the ability to prime would be confirming the clinical benefit. Well, you still would need data to see that the product protects from clinical illness. You wouldn’t really be there.

We haven’t had these discussions, but from just talking here from the cuff, so to speak, I don't think we would go there.

DR. DAUM: Thank you. That’s a helpful clarification.

Thank you very much, Dr. Collazo-Custodio.

Dr. Golding is next and is going to talk about vaccine adjuvants and mode of action for GSK's AS03 adjuvanted H5N1 monovalent vaccine. Dr. Golding, welcome.

Agenda Item: USG Programs and Goals for Antigen-Sparing Pandemic Influenza Vaccines

DR. GOLDING: I think this is a good opportunity to introduce this committee and the audience to the whole concept of using adjuvant in combination with vaccines, because, not only today, but also tomorrow, we would look at the added benefits of adjuvants in the context of prophylactic vaccines for healthy individuals.

I just want to start by discussing adjuvants, what we mean by adjuvants. An adjuvant is a substance that acts to accelerate, prolong, or enhance antigen-specific immune response when used as part of vaccine formulations. Most adjuvants activate early innate immunity.

Why do we need adjuvants? I think there is a major shift in paradigm in the past several decades, with greater emphasis on improving the safety of vaccines. What it means is, translated from a manufacturing point of view and vaccine-design point of view, a shift from the traditional type of prophylactic vaccine that we are all familiar with and we use to vaccinate our children -- which are the whole viral or bacterial vaccines which are either live attenuated or inactivated -- there is now a shift to

highly purified vaccines, subunit vaccines, that are made by a different type of recombinant technology.

Unfortunately, along with this improved purity and safety, we notice a significant drop very often in the potency of these vaccines. Of course, this needs to now be replenished, so to speak, by maybe providing different classes of compounds, which we call adjuvants, which can then help us to bring back the potency of the vaccines, along with the improved safety that we have observed. So adjuvants, as indicated, I think, by Dr. Goodman already, are needed to improve the immunogenicity of recombinant vaccines, increase the breadth of protection, which is very important, especially when we have multiple subtypes or clades, such as in the case of HIV and influenza, and to overcome reduced immune responses in targeted populations, such as the very old or the very young, and, in the case of pandemics, clearly a reduced antigen dose.

I just want to take one step backward to remind us all of the very basic steps during response to vaccination or infections. Very often the exposure occurs in the peripheral tissues, usually in places like the muscle, the nose, or the skin, and the first cells that come and pick up the antigens are those immature dendritic cells, as well as some premonocytic cells.

In addition to processing the antigen, these

dendritic cells have to undergo significant maturation that allows them, then, to migrate through the lymph to the local draining lymph node, where they can present this antigen to the antigen-specific T cells and B cells that can then undergo maturation into effector cells, secreting immunoglobulin and cytokines. This transition from the local exposure to the drain requires significant maturation into antigen-presenting cells, which involves upregulation of multiple costimulatory molecules, HLA, as well as the ability to secrete several types of cytokines that help ultimately in the maturation of the effector B and T cells. This is where we think adjuvants are working.

In order to undergo this type of maturation, the dendritic cells, I think, during evolution have evolved by expressing multiple types of what we call sensors or pattern recognition receptors. Those are receptors that have been evolved to basically sense the environment, sense pathogens, including bacteria and viruses, either outer membrane’s component of Gram-positive and Gram-negative bacteria, flagellin, and also nucleic acids that are typical of either viruses or bacteria. These receptors have been termed Toll-like receptors, NOD-like receptors, RIG-like receptors. They can be either on the surface of the dendritic cells, in the cytosol, or in the endocytic compartment.

But most importantly, once they have been activated, they provide those cells with the signaling required for their maturation into fully functional APC. And it’s really the level of this early APC maturation that has a major impact on the magnitude of the adaptive immune response.

What adjuvants are trying to do is to basically mimic some of the natural ligands of these receptors. I think a good example is the yellow fever vaccine, which is a very potent vaccine that elicits very long-term immunity. It was shown recently by Bali Pulendran that this vaccine actually can activate multiple Toll-like receptors and even cellular RIG-like receptors.

Those traditional live attenuated vaccines brought with them not only the specific antigens, the protective antigens, but also the various ligands that are required to activate the innate cells via these various pattern recognition receptors. Once we move into a more purified vaccine, the adjuvants hopefully can mimic these agonists of the innate receptor.

Let’s look at what we currently have in the pipeline. This is by no means an exhaustive list. I just want to remind you that adjuvant mode of action in general is an important parameter in trying to maybe predict which vaccine will best benefit from which adjuvant. However,

it’s not always fully understood before licensure of vaccines containing adjuvants.

Instead of reading the whole list, I just want to point different classes of adjuvants that are listed on the left and just point out the key adjuvants. We all know that aluminum hydroxide has been a component of multiple vaccines that are currently distributed to millions of children and adults. The AS03, which is a component of today’s vaccine, the Q-Pan, in the BLA, belongs to this class of microfluidized detergents, emulsions, and saponins.

Among the TLR agonists, you will hear about CPG, which is one of the TLR9 agonists, which will be presented in the context of the hep B vaccine.

I also want to point out MPL, which is a TLR4 agonist. It’s a component of the combination adjuvant AS04 that, together with aluminum hydroxide, was part of the HPV vaccine that was licensed several years ago.

This is a more general approach that one has to keep in mind with looking at both the benefit and the risk of adjuvanted vaccines. Clearly we are very interested in enhanced and accelerated immune response. We would like to see this improved in long-term memory and dose sparing. Also improved in the diversity of immune response and increased antibody affinity may contribute to the ability

to get cross-reactivity or cross-protection.

However, we have to be cognizant of potential risks that may also be associated with these novel adjuvants. We already expect to see increased reactogenicity. Once you have a more robust innate response activation, one definitely expects to see more local reaction, including pain, as well as systemic effects, including inflammation, fever, and myalgia. We also have to look out for nonspecific immune activations. They may include immune types of diseases -- they may be either organ-specific or not -- and general inflammatory diseases.

I want to emphasize that it is important to really monitor both the benefits and the risks throughout the lifecycle of the product, all the way from preclinical through early development, licensure, as well as post-licensure. You are clearly going to hear a lot about that today in the rest of the presentations.

Now let’s focus our attention on AS03, which is the oil-in-water emulsion-based adjuvant which is a component of the H5N1 Q-Pan. It forms nanoparticles, 120 to 180 nanometers. It has, as indicated, an oil and a water phase. The oil is made of a one-to-one ratio of squalene and alpha-tocopherol, a vitamin E that is also an immunostimulant. The buffer system provides the water

phase. The polysorbate 80 is the emulsifying agent.

In terms of mode of action, actually GSK conducted a significant number of studies in both preclinical, in mice, and with human cells, including microarrays, and tried to understand what really is the mode of action. What is indicated already is that, unlike the case with aluminum hydroxide, where the antigen is absorbed onto this particular adjuvant, in the case of oil-in-water adjuvants, and AS03 in particular, there is no evidence for direct interaction between H5N1 antigen and AS03 adjuvant. However, the adjuvant and antigen do need to be administered at the same site and within a short time period, preferably together.

The MOA antigen studies in mice -- what are the key findings? AS03 modulates local innate responses in the site of injection -- namely, the muscle -- and the draining lymph nodes. There was demonstration of recruitment of monocytes, dendritic cells, and neutrophils to the muscle, transient chemokine and cytokine production, enhanced antigen loading by APC, increased costimulatory molecules that are required for APC function. NF-kappa B activation was shown using a reporter-based bioimaging system. It was shown that NF-kappa B, which is a master regulator of multiple other immune cytokines, could be shown in the muscle and draining lymph nodes, but not in non-draining

lymph nodes or liver. Therefore, the innate responses in general were transient, within 24 to 48 hours.

In terms of the adaptive immune system, antigen-specific T cells were demonstrated with a mixed Th1/Th2 cytokine, enhanced antibody responses -- IgG1 a little bit more than IgG2. There was also evidence provided for the importance of alpha-tocopherol in contributing to the immune response enhancement against vaccine antigen.

Importantly, in these preclinical studies strong evidence for dose sparing with AS03 was also demonstrated.

In addition, GSK, in contracts with Viroclinics, conducted multiple preclinical studies in the ferret model, which is one of the most sensitive animal model for influenza, that was shown to have a similar distribution of the sialic acid, the alpha-2,6 and alpha-2,3, similar to human, in the lower and upper respiratory tract, and has been shown to be a fairly good model for influenza disease.

Those models can be used to look both at pathogenicity and vaccines. Through Viroclinics, they conducted multiple studies with challenge of highly pathogenic, either homologous strain, the A/Indonesia clade 2.1, or heterologous strain, either the Hong Kong clade 0 or the A/Vietnam clade 1 H5N1. All animals were evaluated for lethality, fever, body weight, gross pathology in the lungs, virus loads in the upper respiratory and lower

respiratory tract, both by PCR and PFU in MDCK cells, as well as monitored for virus shedding. The immune responses were HI and neutralizing titers against homologous and heterologous strains.

What were the results of these studies? Animals that were vaccinated twice with the Q-Pan vaccine -- the human dose -- were protected from lethality following challenge with either homologous or heterologous clade 0 and clade 1 strains. The protected animals had much reduced lung pathology, both macroscopic and microscopic findings.

In addition, the vaccinated animals had lower viral loads in the nasal washes and the lungs, and virus replication in MDCK cells correlated well with disease pathology and inversely correlated with vaccine dose. The PCR data was less correlative.

Importantly, immunogenicity was supportive of the challenge outcome.

I just want to summarize.

In terms of the preclinical studies of H5N1 AS03 vaccine, the AS03 mode of action at the cellular receptor level is still not fully understood. However, preclinical studies in mice and human cells demonstrated enhanced antigen uptake, APC function, and local cytokine release. The innate immune activation was demonstrated to be

transient and mostly localized to the site of injection and draining lymph nodes. Preclinical studies with AS03, in combination with TIV or H5N1 monovalent inactivated vaccine, demonstrated significant augmentation of HI titers and dose sparing.

Ferrets vaccinated with the Q-Pan H5N1 vaccine were protected from lethality following challenge with either homologous or heterologous H5N1 virus strains, and significant reduction in viral loads in the upper and lower respiratory tract, as well as lung pathology.

Importantly, the preclinical studies supported the intended human dose of Q-Pan, which is 3.75 micrograms, plus AS03, .5 mL.

DR. DAUM: Thank you very much, Dr. Golding.

We are starting to get into time problems, because our speakers have prepared more material than their time allows. I would like to ask subsequent speakers to be mindful of that. It’s not an airplane day, but still we would like to run on time if we possibly can.

Is there clarifying question or two for Dr. Golding before we move on? We are behind.

(No response)

Thank you very much, Dr. Golding, for your presentation.

We’ll call on Dr. Robin Robinson now, from BARDA.

He will talk about USG programs and goals for antigen-sparing pandemic flu vaccines. Welcome.

Agenda Item: USG Programs and Goals for Antigen-Sparing Pandemic Influenza Vaccines

DR. ROBINSON: Good morning.

It was only a short eight years ago, which seems like a lifetime, that we meet at IOM, in June of 2004, and talked about pandemic preparedness and all the many different things, and Pranosho Pan (phonetic) warned us that we really do need to move forward.

Lo and behold, that year, Jesse Goodman had to carry the load in which we lost one of our major manufacturers' influenza seasonal purposes, and lo and behold, we saw the reemergence of H5N1 in Asia, as we thought we had dispensed with it in 1998 with the culling of the bird markets. We saw the H5N1 vaccine clinical results in the next year, in which it was not going to take 15 micrograms of antigen, but 90 micrograms -- six times more. We have less vaccine manufacturing in the US. And lo and behold, we have a hurricane that wakes everyone up.

Those converging events led to the US issuing a strategic plan for pandemic influenza, the Department its own pandemic influenza plan and implementation plan. Many people have read these, and they know that they are in extreme detail in many regards, if you take them in toto.

Specifically for vaccines, there were two goals that were really expectations that gave us the plan to go forward. One is to establish and maintain a dynamic pre-pandemic influenza vaccine stockpile for 20 million persons in the critical workforce. That led to the H5N1 stockpiles, which I'll talk about a little bit later on. Second was to provide pandemic vaccine to all US citizens within six months of a pandemic declaration. It was two doses, therefore 600 million doses.

That set us in motion with the unifying principle that what we do for pandemics must be in the context of seasonal influenza preparedness -- and we certainly have gone forward -- but also other hazards.

How did we implement this? First, we needed to fortify what we were doing with our existing vaccine capabilities, that being our egg-based. Secondly, with NIH and, to a certain extent, the DARPA at DOD, BARDA worked very hard to actually support development of better influenza vaccines that can afford greater manufacturing surge capacity, with cell-based vaccine development, recombinant molecular vaccines, adjuvants for dose and antigen-sparing purposes, and universal flu vaccines. We have made progress in every area there, and the realization of being able to address universal flu vaccines is at our hands now to be able to ask the right questions, in fact.

Part of that set of implementation goals was to establish the pre-pandemic vaccine stockpile, which has been done, and then to expand our domestic manufacturing capacity by retrofitting existing egg-based facilities and also establish new facilities, which resulted in the cell-based facility in North Carolina.

Graphically, this can be looked at as a multistep process in which we have fortified the egg-based vaccines, we have moved forward with our cell-based vaccines -- and hopefully those will be coming online soon -- and investments in recombinant vaccines, both at NIH and with BARDA, and hopefully moving forward with universal flu vaccines.

Antigen-sparing vaccine technology touches all of those, whether they be egg-based, cell-based, recombinant, even including the universal flu vaccines. That has led to our mantra: More and better vaccines sooner, “better” meaning that we really do have a better vaccine, not just a better way of producing it.

If we go forward, we actually knew that we needed to increase our ability to have vaccine available sooner. In 2009, we relied on our existing capacities. We predicted that 20 to 24 weeks was when we would actually have vaccine available. Sure enough, it showed up right at that point.

What we see against the unabated pandemic vaccines -- we're on the descending side of the pandemic wave. What we would like -- this is what we see as the idealized pandemic wave, where we can actually reduce the number of cases of influenza illness.

As we move forward with our new vaccines and domestic manufacturing facilities, with improved vaccine manufacturing initiatives, where we have a shorter time to actually have vaccine strains available for the manufacturers, we have better potency assays that shorten the time, and sterility assays, then we may be in a world in which egg- and cell-based vaccines with adjuvants and recombinant vaccines with adjuvants can be available before the peak of the pandemic. Certainly the pre-pandemic vaccines, if we have them, that are available against the vaccine that causes the pandemic may actually be applicable.

With universal flu vaccines, of course, I think we all know that would transform not only pandemic influenza preparedness, but also seasonal. In some people's eyes, it actually may provide a priming dose. Every five years, if you take a universal flu vaccine, that is your primer then, and we actually may need only one dose of a booster vaccine, which would be the pandemic vaccine, whether it be egg, cell, or recombinant vaccines with

adjuvants. Again, it’s being able to get ahead of the peak and actually reduce that mortality so that we have a more idealized pandemic response.

To be more specific, the Department has supported multiple projects since 2007 with H5N1, in 2009 with H1N1, for advanced development of pandemic influenza vaccines with adjuvants, and many different types of adjuvants, towards US licensure. That has always been our goal, not just to have it available under EUA, but also to move those towards licensure. This represents one of those milestones today.

There are candidates at various stages of development. Q-Pan represents one of the more mature. There are others that are mature and those that are still in Phase I and Phase II studies.

Multiple study results, not just of Q-Pan, but of other adjuvant-containing H5N1 vaccines from academia, the government, and vaccine manufacturers, have shown that different oil-in-water emulsion adjuvants confer additional properties on the flu vaccines. That has been spoken now repeatedly about antigen- and dose-sparing effects. That has been shown -- 12-fold difference between an antigen-alone vaccine and with H5N1 versus -- 90 micrograms versus 3.75 micrograms with an AS03 adjuvant, for example.

But also there may be dose-sparing effects.

Instead of having two doses, there may be populations that actually are able to go forward with just one dose. Hana presented that cross-strain protection has been observed. In some cases with other vaccine adjuvants and antigens, there may be a prolonged prime-boost immunity, from one of the NIH studies in which you actually could see up to 10 or 12 years -- with a person that has been immunized with a vaccine with these adjuvants, that later on they can respond very well to a booster, a single booster, with the vaccine with the adjuvant.

Lastly, since we don't have all the manufacturers in the US having mature adjuvant programs, we have within NIH and the manufacturing industry done something that many people didn’t think could be done -- that is, to all come together with an interim solution using adjuvants in what we call mix-and-match studies, to actually take adjuvants from one company, mix it with antigen from another company, and can it provide an immunogenic response? Certainly with H1N1 the results are there. It can do that. With H5N1 antigens, the preliminary interim data say that two different adjuvants can work with another antigen from another company.

So at least in the interim, if something happened today, we would have those data that would actually inform us as we go forward. Hopefully we will have all of our

products going forward with an appropriate adjuvant as needed.

Our vaccine stockpile -- the HHS, BARDA manages that, established it starting in 2004. It was completed in 2008. We have four different strains of H5N1 represented. There is a fifth one that can be available. It has been made and just needs to be put in there, with two different adjuvants in our stockpile. Those adjuvants were available if needed in 2009 during the pandemic. But we have enough antigen alone to meet our 20 million-person need, but also with adjuvant, it could be several hundred million.

Every year the Department uses the CDC's influenza risk assessment tool to evaluate what the new strains are that need to be added to the stockpile. We did discuss at great length the H32N variant. We decided that we needed to do the clinical studies and see what the results are, but we would not move forward with bulk antigen at this time.

The potency of the bulk vaccines, antigen lots remains greater than 75 percent after five to eight years, and the bulk adjuvant lots, nearly 100 percent after four to five years. That's actually unbelievable. The reason why is because the vaccine manufacturers routinely kept vaccine antigen, even as a bulk form, only for about 18 months. Every day that we have these vaccine lots tested

and kept at the manufacturers and we go another day, we set a record. I think, for me and probably some of you in the audience, that is an astounding feat. But they are there. We intentionally did not put those vaccines into vials because we thought that the potency would have dropped. So we still have those vaccine antigens, some from 2004, that are available with the Vietnam H5N1 strain.

Pre-EUA packages have been submitted by BARDA to the FDA this year for the stockpiled vaccine and adjuvants. If we had to use them, the FDA has those available to review and move forward, if necessary.

Vaccine distribution would be through the central distribution system managed by CDC, very similar to what we saw in 2009.

Lastly, the US government is committed to working with the vaccine manufacturers, including GSK, with their H5N1 vaccine with AS03 adjuvant. The US government -- not only HHS in the form of CDC, FDA, and BARDA, but also DOD and others -- will work with the flu vaccine manufacturers to continue our partnership on post-licensure activities for not only the pandemic, but for seasonal purposes, with safety and performance tracking, planning the future tracking systems for influenza vaccine safety and effectiveness, and executing these tracking systems during the inter-pandemic times to get needed data for seasonal,

but also as a needed exercise as we go forward when we have to use these for a pandemic.

Dr. Joe Bresee will tell us much more about the vaccine effectiveness studies.

I'll stop there. Thank you.

DR. DAUM: Thank you very much, Dr. Robinson.

Clarifying questions at this time? We can return to topics this afternoon during our discussion period. Dr. Marcuse.

DR. MARCUSE: Just one question. What, if anything, do we know about the safety and efficacy of oil-in-water emulsions as adjuvants in persons under age 18?

DR. ROBINSON: There have been studies that have been done. What we do know about the safety is that it seems to be well tolerated, even in small children. Some of the manufacturers can tell you more about that. There have been studies in small children, 36 months and younger, in which the vaccine was not only well tolerated for safety purposes, but also was very immunogenic as compared to the antigen-alone counterparts.

So there have been studies, and certainly, as we go forward, there will be more studies done.

DR. DAUM: You might wish to return to this topic this afternoon. I think it's an important one.

Any other clarifying questions?

(No response)

We thank you for your presentation.

Certainly not least, but last, before the break this morning, is Dr. Bresee from CDC, who will talk about pandemic vaccine effectiveness experience during the H1N1 pandemic.

Agenda Item: Pandemic Vaccine Effectiveness: Experience during H1N1 Pandemic

DR. BRESEE: Thanks very much.

I guess we're only about five minutes from break, and so with the Chair's agreement -- I meant to give two talks. One is an update on H5 epidemiology and clinical characteristics, which is a short talk. The other is the more probably salient talk to this discussion, and that is a review of our effectiveness studies towards answering the core question as to whether CDC's effectiveness platforms can be brought to bear to answer the question of measuring product-specific vaccine effectiveness during a pandemic.

With the Chair's agreement, I'll skip the first part if you want and just summarize it in one slide, and maybe come back to it at the end of the talk, should we have time, and focus on the second part that's probably more salient for your discussions.

DR. DAUM: Can you get both done in 20 minutes?

DR. BRESEE: As you prefer. I can keep both

under ten, if you prefer.

DR. DAUM: Well, you have 20, and we want to hear your information.

DR. BRESEE: Okay, fantastic. I'll just do the whole thing then.

We'll start with the H5 part. H5 emerged in 1997, as you guys know, in Hong Kong. It went away, reemerged in Hong Kong in a family that visited Fujian province and was exposed to sick poultry there. It caused two cases and one death.

But the main epidemic that's ongoing now started late that year and spread initially to surrounding southern Asian countries, but then westerly towards Europe and Africa, as you know. To date, there have been 608 confirmed cases in 15 countries and a very high case fatality rate, which is maintained around 60 percent throughout the epidemic that has lasted now nine years.

Most cases are sporadic cases of people -- mostly children and young adults -- who are exposed to sick poultry through care of them or through slaughtering practices. Over time there has been a clear development of a wintertime seasonality, both in terms of poultry outbreaks and also human outbreaks. The risk factors that were appreciated early in Hong Kong, in 1997, persist, and that is direct and close contact with sick and dead

poultry, visiting a live poultry market. Clearly about 20 percent of the cases that are reported have no discernible risk factors, but those cases are generally in populations or neighborhoods that have poultry markets available to them. The suspicion is that the occult exposure is actually the exposure we always see, and that is the live poultry market exposure.

Risk factors for severe disease continue to be late presentation and delayed treatment with oseltamivir.

Most are sporadic, but there are clearly case clusters of illness. Most of the clusters arise from single exposures to a flock of sick birds among a family and multiple people get infected. There are cases of clusters associated with human-human transmission, mostly with a single instance of human-human transmission, two clear clusters that have shown at least two generations of transmission between humans.

This is a slide that’s not complete. On the right-side, 2012 only has the first month. But it illustrates three, I think, important epidemiologic features of H5 disease in humans. This is a histogram of all the countries over time that have reported cases. You see a clear wintertime seasonality has developed. The second thing you see is that in countries with endemic poultry disease, like Egypt or Indonesia -- Egypt is in the

gray, Indonesia is in the yellow -- you see the ability of the virus to cause intra-peak illness, maybe summertime illness. The third feature is that you see the consistently high case fatality ratio, illustrated there in the red line.

These are the countries that have reported human cases. No surprise here -- mostly in Asia, but again the westerly spread in 2006 to 2008 resulted in cases in Africa, Eastern Europe, and Central Asia and the subcontinent. The only place that persists, really, in endemic poultry disease and sporadic cases is Egypt.

Good news: This last year there were only six countries that have reported human cases since the beginning of this year. That’s about the same as last year, in which there were five countries that reported cases. Only 30 cases this year, which is a decline of about 37 percent from last year. But the case fatality ratio remains quite high.

This is just to remind us that, in fact, the clades that are occurring in humans right now continue to be a variety of clades, including clade 1 and 2 viruses, but a bunch of sub-clades as well, which highlights the challenge of developing vaccines against this virus as a pandemic preparedness activity.

That was the whole thing. The summary:

• The epidemiology and clinical characteristics of H5N1 in poultry and in humans is largely unchanged in recent years. Most cases are sporadic. Most cases are in children and young adults with exposures. Most of the relevant exposures are exposures to sick and dead poultry. Seasonality continues to be observed in colder periods.

• The good news is that there are relatively fewer cases in the last couple of years compared to previous years. We hope that’s a trend. But clearly we’re coming into the high season right now

• We believe and most people believe that confirmed cases are clearly an underestimate of the total number of cases, though the absolute risk, or the real risk, of acquiring this infection is higher than what we have observed.

• Finally, the risk remains. The risk remains both in terms of poultry outbreaks and the economic disturbances associated with those. But to humans, the risk remains of ongoing, sporadic disease and also, as the virus continues to evolve, the risk remains of a pandemic development from this virus.

Let me turn to what I’m meant to talk about, and that is a summary of our vaccine effectiveness program at CDC, or our collaborations to do that, towards answering the question, can we produce product-specific VE estimates

during a pandemic? This is a very 30,000-foot summary that I'm going to give you. I'm going to focus on those attributes of the systems that I think are most relevant to that discussion, but I'm happy to talk about any of the attributes or any of the data as well. You'll see glimpses of data, but not much.

We started thinking about VE estimates at CDC back in 2003-2004. The epidemic in that year was associated with high rates of mortality in kids. So we set up studies, initially with something called the new Vaccine Surveillance Network and then with the Emerging Infections Program, to estimate the value of vaccine in the populations that ACIP was developing policy for. As you recall, during that time ACIP was expanding the policy recommendations to include initially young kids and older kids -- and all kids. The goal of the vaccine effectiveness evaluations during that time was to try to set up studies so that we could evaluate how well the vaccine was working in ACIP target populations.

We have had a variety of collaborations over this nine-year period of time, listed here sort of in a cartoonish form. What I want to point out is that the current iteration of these collaborations is something we call the US Flu VE Network. I said two because we have had two iterations of this. I'll talk about the current one,

but I'll talk about the previous one in relation to the 2009 pandemic estimation.

The US Flu VE Network, the current iteration -- the primary purpose is to estimate vaccine effectiveness for prevention of health-care visits due to influenza, by age group if we can and by type and subtype if we can. The network and the collaborations that we have done on VE have actually never been designed or intended to develop product-specific estimates. The public health question is, do vaccines work in the groups that we intend them for? It has never been a product-specific question. We haven't designed the studies to look at those issues. I'll explain how that becomes an important issue in a second.

The US Flu VE Network has five sites, as you see on the map, currently. Dr. Piedra here is a collaborator in the Texas site in the last couple of years.

The sites enroll all children and adults with medically attended acute respiratory illness.

An overview of the methods: The studies are done as prospective case-control studies. The cases are medically attended acute respiratory illness that are confirmed to be influenza using an RT-PCR designed by CDC. The controls are test-negative controls -- so the medically attended respiratory illnesses that come in, are tested for flu, but found to be negative. Those are used as our

controls.

Vaccination status is confirmed through medical records, but also collected through self-report. An immunized person in this study is defined as a person with MAARI who received at least one dose of vaccine at least 14 days or more before their onset of symptoms.

The analysis is done as analysis is always done. I wrote this just to point out the fact that a lot to the confounders that are problematic in observational studies of VE we have tried to account for in this model. The VE is estimated through a logistic regression model, and the variables you see there are included in the model.

Two quick data slides just to show you the types of data that are potentially available in this system. These are data from this last season. These data actually have never been viewed in public until right now. We presented preliminary data in June ACIP, and there is very little change, really, to the final data.

But what you see is, on the far right side, a VE against influenza virus infection, the medically attended virus infection. In most years we can get that by subtype or type -- not all years, but in some years when we have enough disease and the vaccine works well enough and we have enough coverage, we can measure vaccine effectiveness, not only against flu, but against flu by subtype or type.

Similarly, the studies are designed to measure VE against age groups that are relevant to policy discussions. So in this last year, as you see, we were able to measure a VE that is significant against the four age groups listed here. We rarely, to be honest, can measure VE for elderly people specifically. We just don't have enough in the system. So we often present the data like this. Over-50-years is our top age group.

We used the first version of this group, which had four sites, in 2009 to address the issue of whether pandemic influenza vaccine works. This is just one slide I’m going to show from this. It shows one of the key features that I’m going to harp on repeatedly. In fact, these systems were able to be mobilized to measure a vaccine effectiveness of 56 percent during the pandemic, for pandemic flu vaccines as a class of products. But importantly, the low numbers in our study sites prevented demonstrating significant protection for many of the subgroup analyses we normally get for seasonal vaccine VE estimates, including some ages and some vaccine types. The reason is in the figure you see below that. You see that the dark bars represent flu positive cases that occurred in our study sites that were surveyed in our study sites. The red line represents vaccine coverage levels in the study sites. As you know, vaccine arrived in the fall, but a lot

of the disease occurred before that. The same was the case in our study sites, where the lion's share of disease occurred before vaccine was available. So what you did was effectively reduce the sample size eligible for het study, thereby limiting the ability to create estimates for subgroups.

The other way we measured vaccine effectiveness historically and during the pandemic was using a collaboration called the Emerging Infections Program. This is a program operated by CDC that does lots of things. Among them, we conduct population-based surveillance for laboratory-confirmed flu hospitalizations each year. We can use this to bring to bear to do a case-control study to measure VE each year in the populations they study. We did this during the pandemic.

In this, the cases are laboratory-confirmed hospitalized patients. The controls are community controls that are called on the phone.

This is a big system. It represents 7 percent of the US population and is big enough to where classically we can look at age group-specific VE in this system against severe disease in this case.

This is how it worked in the pandemic. This is the same sort of slide I showed you a minute ago for the US VE Network. The bars here represent the flu positive cases

that occurred in these study sites during the fall of the pandemic. It's hard to see, but the peak of that curve really occurs around early October, declining after that. We enrolled our first patients in the EIP VE around the first week of December, long after the bulk of the disease had occurred.

In this system, actually, despite that, we were able to measure an overall VE against pandemic disease from pandemic vaccines. But the ability to do subgroup analysis, age group or vaccine type analysis, was severely limited because of the sample size available to us because of the late arrival of vaccine in these sites.

The other thing we did during the pandemic, just to finish this part, was we took advantage of opportunities. One of the opportunities arose in the state of Maine. Maine was interesting because they distributed all their vaccine for the pandemic through school-located vaccine programs. The other reason they are interesting is -- and I'll tell you in a minute -- they had very late disease.

So we engaged in two studies, one with the Maine CDC to look at the effect of the vaccine on preventing absences of students and their teachers, and found the vaccine was indeed effective even against this nonspecific outcome, and also looked at VE against laboratory-

confirmed, PCR-confirmed influenza in the most populous county in Maine, and again found very consistent VE estimates.

The reason Maine was interesting to us was not just the chance to look at a school-located vaccine program and see how well it worked. It was because of this. This is the same sort of graph I have shown you three times now. The red line rises in the middle of the epidemic curve rather than at the end of epidemic curve in this case. So there is the capacity during a pandemic to rev up new sites, new studies to answer the VE questions. Maine was perfectly suited for that because of the late arrival of the pandemic virus in Maine and the relatively aggressive and early vaccine use in Maine. So there were more eligible cases and controls available to us.

The key points from these three lessons, I think, are these:

• First, that we do have a robust way to measure VE in the US. Most seasons, we're also able to measure not only overall VE, but also subgroup VE analyses.

• Second, we're able to formulate rapid intra-season VE estimates using these systems. These are important to us for communication purposes, both for seasonal and during a pandemic.

• We have sites that are geographically

dispersed. This mitigates the problems of having missed disease because you are only in one or two sites or having late or early disease in some sites that you miss. We think we have done a good job of spreading the sites around well enough so that wherever disease occurs, we would pick it up and be able to measure effectiveness of the vaccine against it.

• During the pandemic, the sites were great. They mobilized quickly and effectively, despite the fact that it wasn't in their contract. They were able to initiate special projects and address VE in special populations on the fly, which is very helpful. But the late arrival of vaccine relative to disease occurrence severely limited the ability to do subgroup analysis. I think that's relevant for this discussion.

Let me go back to this. These are the attributes. We do have a robust system. With a high attack rate that one might expect during a pandemic, we're sure that we can measure VE. The problem again is that the temporal overlap between disease and vaccination that's inherent in the way the vaccines are produced now and the way that pandemics are likely to arise will severely limit the power to look at subgroup analysis, including product-specific VE.

We clearly mobilized the systems to address the

needs in the pandemic. The concern clearly is, with an H5 pandemic, with a higher rate of severe disease, including mortality, the ability to mobilize these sites, much less new sites to expand the network, will be severely limited.

We have geographically dispersed sites so we can capture new cases. However, the fundamental problem is that geographic location of sites might not reflect the distribution of product in a way that makes product-specific VE estimates possible.

Finally, while we do capture vaccine product information, we miss 30 percent of it right now. We can change that. We can help that. That’s a minor problem, but a current problem.

Conclusions:

• CDC plans to estimate overall and age group-specific VE for pandemic vaccine during the next pandemic. We plan to use primarily existing seasonal program platforms to do that.

• CDC cannot guarantee that product-specific VE estimates will be derived from its work during the next pandemic. We can’t for two fundamental reasons: the sample size issues that I talked about, for a variety of reasons, and the vagaries of the distribution of vaccine products relative to where we work that we can’t control.

• That said, we’ll continue to plan for how we’re

going to measure VE during a pandemic. This may change. As we go through these iterations, if the group feels that this is a really important thing to do, we can think about whether we can modify our systems to do so. But right now, in the foreseeable future, I think, while it's possible to do this, I won't promise that we can do it, and I think it's unlikely to happen that we could get product-specific information.

Thanks.

DR. DAUM: Thank you, Dr. Bresee.

We have a minute or two for clarifying questions on the presentation. I'll start off with one, I guess.

Would you mind putting the slide back up that's entitled -- you said it's the first time you have shown these data in public --

DR. BRESEE: I was afraid you were going to make me show that again.

DR. DAUM: Sorry. But I do have a question about them. They are very interesting.

I think you said to get in this table, you had to have at least one dose of vaccine.

DR. BRESEE: That's right.

DR. DAUM: It's a pediatric question, I guess. There were some data about young children. This may be not the right slide. There were some data about young

children, efficacy. If they only had one dose, I guess the question is, are you surprised by that estimate? How many of them only had one dose?

DR. BRESEE: The statement was a general statement that to be vaccinated, they have to receive one dose. In fact, we analyzed kids 6 months to 8 years old as a two-dose vaccine estimate. The 58 percent is actually a two-dose estimate -- an appropriate-dose estimate, either one or two.

DR. DAUM: That clarifies my question.

DR. BRESEE: We can analyze it both ways, but this includes received vaccine as ACIP recommended it.

DR. DAUM: So if it's feasible and mathematically possible, it would be very interesting to know the efficacy after one dose.

DR. BRESEE: It’s lower. We don't have enough cases to have significant estimates, but the point estimates are universally lower in that group.

DR. DAUM: Thank you. Others? Dr. Marcuse has a question.

DR. MARCUSE: If you have five study sites across the US, has it been impossible to work with those sites to perhaps divide vaccines up among them, and therefore be able to do it? It’s just not clear to me why that’s so impossible.

DR. BRESEE: Two things, I guess. It has never been part of our reason to do these studies, so we have never actually addressed that issue. Our public health goal is not to do that, I would say.

I would also -- and maybe I would defer to Melinda -- I think the possibility of us convincing large medical groups and centers to use a single vaccine or a couple of vaccines is probably pretty limited, though maybe Tony or Melinda could comment on that.

DR. DAUM: But you raise a good point. We can come back to it this afternoon in the discussion.

Other clarifying comments? Dr. Gellin.

DR. GELLIN: Joe, I have one for you that I'm going to ask the company later. Since the indications for this are for people who are at increased risk of exposure, in the United States, do you have a sense of how we would look at that?

DR. BRESEE: I don't have a sense. I think there were some efforts in the 2006-2007 pandemic planning guidance, when it was discussed, to try to estimate the groups that might be eligible for the vaccine, including those groups that are exposed.

There's also a current effort under way at CDC that's in its first steps, really, to try to estimate the number of people that are occupationally exposed to H5

viruses, either in the lab or potentially as rapid responders to international or domestic outbreaks. I don't know what that number is right now. It’s not huge, but I don't know what “not huge” means.

DR. DAUM: Thank you very much for your presentation.

We are going to take a 15-minute break. It’s 10:15 by my clock. At 10:30 the sponsor’s presentation will begin. Please be back and ready to go at 10:30.

(Brief recess)

DR. DAUM: Welcome to the late morning part of the meeting. We’ll continue until lunchtime and ask our sponsor, colleagues at GlaxoSmithKline, to now present their side of this presentation. We have Dr. Donna Boyce, Dr. Bruce Innis, and Dr. Felix Arellano presenting.

It’s now 10:30. We’re running ten minutes late, so we will ask you to please keep to the allotted amount of time.

Ms. Boyce, welcome.

Agenda Item: Sponsor Presentation

MS. BOYCE: Good morning, Mr. Chairman, members of the VRBPAC, FDA, and guests. I’m Donna Boyce. I’m the head of regulatory affairs for vaccines, North America, for GlaxoSmithKline. It’s my pleasure to introduce our pandemic influenza A virus monovalent adjuvanted vaccine,

hereafter referred to as Q-Pan H5N1.

I will introduce the candidate vaccine and the proposed regulatory pathway. Dr. Bruce Innis will present the immunogenicity and effectiveness data. Dr. Felix Arellano will present the safety data and pharmacovigilance plan. Then I'll return to conclude the presentation.

As you heard from Dr. Robinson this morning, the US Department of Health and Human Services has encouraged influenza vaccine manufacturers to develop pandemic vaccines. As a global influenza vaccine manufacturer, GSK recognizes our responsibility to support pandemic preparedness. So in partnership and under contract with BARDA, GSK has agreed to develop and to submit for US licensure an H5N1 influenza virus vaccine with antigen-sparing potential for inclusion in the national stockpile. The candidate vaccine is intended to fulfill this contract. Under the contract, Q-Pan H5N1 will be distributed by the US government, who will determine the use of the vaccine.

The contract with BARDA specifies the following criteria for the pandemic H5N1 vaccine:

• It must have an acceptable reactogenicity and safety profile.

• It must be able to rapidly induce protective immune responses in immunologically naïve persons.

• It must be antigen sparing.

• It must be able to be rapidly produced using existing facilities and processes.

The proposed indication is for active immunization for the prevention of disease in persons 18 years of age and older who are at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine. The vaccine is given in a two-dose series by intramuscular injection. The doses are given approximately 21 days apart.

Let me give you a bit of background on our seasonal and pandemic egg-based influenza vaccines, which are relevant for understanding the development of Q-Pan H5N1.

GSK manufactures two seasonal influenza vaccines, FluLaval and Fluarix. FluLaval is manufactured in Quebec, Fluarix in Dresden, Germany. The two processes are similar, but not identical. Each process yields split-virion inactivated influenza antigens. Both vaccines are licensed and distributed in the United States. FluLaval is licensed under accelerated approval. Fluarix is traditionally approved.

In this presentation, vaccine manufactured in Dresden has a D prefix and vaccine manufactured in Quebec, a Q prefix.

Note that quadrivalent formulations containing

two A and two B components, referred to as QIV, for both Fluarix and FluLaval are currently under review by CBER.

GSK also manufactures AS03 adjuvanted H5N1 and H1N1 pandemic vaccines in Quebec and Dresden. The antigen contained in the candidate vaccine is manufactured in Quebec using the FluLaval facilities and processes. The Quebec-based antigen was selected to fulfill the BARDA contract as it’s geographically accessible for distribution in the US.

As part of GSK’s pandemic preparedness plan, Q-Pan H5N1 vaccine has been licensed outside the US in 30 countries, shown in orange. Note that GSK’s Dresden-based D-Pan H5N1 vaccine is also licensed in Europe and Australia. In February 2012, the vaccine was submitted for licensure in Canada and the US.

GSK also developed and licensed AS03 adjuvanted H1N1 vaccines, manufactured at both our Dresden and Quebec facilities, in response to the 2009 H1N1 pandemic. These vaccines were registered in more than 50 countries, based on clinical experience in more than 10,000 subjects. Importantly, during the pandemic more than 90 million doses were administered, of which 60 million doses were manufactured in Quebec. As a result, extensive safety and effectiveness data have been generated. Lessons from the H1N1 experience have been considered in the development

plan and the proposed pharmacovigilance plan for the candidate vaccine. You will hear more about this during today's presentation.

The candidate vaccine is supplied in two separate vials. One multidose vial contains the H5N1 antigen, which consists of purified, detergent-split inactivated influenza type A virus. The antigen is manufactured in Quebec according to the FluLaval seasonal influenza vaccine manufacturing process. The second vial contains GSK's oil-in-water emulsion adjuvant system, AS03, which includes alpha-tocopherol, squalene, and polysorbate 80. AS03 is manufactured in Belgium.

The antigen and adjuvant are mixed in a one-to-one volume ratio on the day of administration to yield a 10-dose vial presentation. The standard adult dose is 3.75 micrograms of adjuvanted hemagglutinin per .5 mL. The final vaccine contains thimerosal at a concentration of 5 micrograms per dose.

Regarding the regulatory pathway, as discussed at the February 2012 VRBPAC and as presented by FDA this morning, there are several potential pathways for licensure of pandemic influenza vaccines. GSK initially pursued traditional approval of the candidate vaccine, but upon review of the file, it was agreed that licensure of Q-Pan H5N1 would be sought via accelerated approval. Under the

selected pathway, if the adjuvanted pandemic vaccine is manufactured according to the same process as the seasonal vaccine which is licensed under accelerated approval, then licensure may be granted under accelerated approval based on acceptable safety and immunogenicity data. As you will see during today's presentation, the prespecified immune criteria have been met, and the safety profile supports the proposed indication.

The committee is being asked to discuss approaches to verify clinical benefit of Q-Pan H5N1 as required under the accelerated approval regulations. GSK proposes to fulfill this requirement using efficacy data generated with FluLaval. In other words, when the clinical benefit of FluLaval is confirmed, effectiveness of the candidate vaccine may be inferred. In fact, the efficacy data of FluLaval has recently been demonstrated in a pediatric clinical endpoint study, Q-QIV-006. These data are currently under review by FDA and, with their agreement, will be presented.

Lastly, and in accordance with CBER's 2007 guidance, GSK expects to work with the US government to collect safety and effectiveness data when Q-Pan H5N1 is used.

The clinical development plan for the candidate vaccine was extensive. The results of the pivotal

immunogenicity and safety studies, the effectiveness studies, and the integrated safety summaries submitted to support licensure will be presented during today's presentation. In addition, and with CBER's permission, Dr. Innis will present the results from two pediatric efficacy studies, Q-QIV-006 and Q-Pan H1N1-035, which provide evidence of clinical benefit of the candidate vaccine.

Now I'd like to introduce Dr. Bruce Innis, who will present the immunogenicity and effectiveness data.

DR. INNIS: Thank you, Donna.

My presentation will be divided into three parts. We'll discuss the rationale for the addition of AS03 to Q-Pan H5N1, the key immunogenicity data, and lastly, clinical endpoint data from vaccines manufactured using the Quebec process.

First, I want to briefly summarize the CBER immunogenicity criteria that were used as surrogate endpoints reasonably likely to predict benefit. There are two parameters that were routinely measured in the clinical immunogenicity trials:

• The seroconversion rate, which is defined as a fourfold increase in hemagglutination inhibition antibody titers, unless the subject is, in fact, seronegative at baseline. Then it represents an eightfold increase. There are acceptance criteria articulated in guidance published

by CBER in 2007. The lower bound of the confidence interval for this parameter should be greater than or equal to 40 percent in adults and 30 percent in elderly adults.

• In addition, there’s what we call the seroprotection rate, which is the proportion of subjects vaccinated who have achieved an HI titer equal to or greater than 1 to 40. The acceptance criteria are shown.

Why are we focusing on 1 to 40? I direct your attention to the text box at the bottom of this slide, which is in all of the prescribing information circulars that are approved by CBER for inactivated influenza vaccines in the United States.

Donna Boyce told you that a pandemic vaccine optimally should be effective at antigen-sparing doses. You heard this morning that the licensed H5N1 vaccine without adjuvant and formulated at 90 micrograms of hemagglutinin per dose is weakly immunogenic. The prescribing information indicates that healthy adults 18 to 64 in clinical trials of this vaccine achieved a geometric mean titer response following the second dose of 1 to 28, a seroconversion rate response of 43 percent, and a seroprotection response of 44 percent.

In this development program we set out to develop a product that would be substantially more immunogenic. We set aside the possibility of using whole virus absorbed to

aluminum, which was already licensed by our company in Europe, because it had limited antigen sparing and, instead, turned to our portfolio of novel adjuvants and, among them, selected AS03, because it’s fully compatible with the split-virion antigen, it’s amenable to stockpiling and surge production -- surge production meaning at least a billion doses in a six-month period -- it is antigen sparing relative to the licensed vaccine in preclinical studies, and you will see the data that show that it affords enhanced immunologic priming after a single dose and strong homologous responses to two doses.

I mention parenthetically cross-reactive responses. These were also assessed. I’m not presenting the data, but we have data and can share those with you this afternoon if you have questions.

You have heard from Dr. Hana Golding of FDA that AS03 elicits an enhanced transient, local, innate immune response. This conclusion comes from characterization studies done *in vivo* in mice and *ex vivo* using human cells. You have heard also that coinjection of AS03 in the antigen is necessary for the effect. There is a transient innate immune response that is activated at the site of injection and in the draining lymph nodes, and this accounts for both the injection site reactions, which are greater than plain antigens, but also the potent humoral and cellular adaptive

immune responses that were characterized during these studies.

You have seen this slide before. There was a very large and comprehensive development program. I will be speaking about three immunogenicity trials: an antigen dose-finding trial in D-Pan and then two pivotal immunogenicity trials with Q-Pan. I will briefly describe the field effectiveness studies that were conducted in Canada, where Q-Pan H1N1 represented 95 percent of all doses distributed in Canada.

In addition, there are two randomized clinical trials that we will describe to you to frame your discussion this afternoon of approaches to confirming clinical benefit of the candidate vaccine.

Let’s turn to the immunogenicity data. The antigen dose selected for D-Pan development, which began in 2006, was used for Q-Pan. The Phase I trial for Q-Pan commenced in 2007.

This is a plot of seroconversion rate responses following dose 1 and dose 2. Healthy individuals in Belgium, 50 subjects per group, were randomly allocated to receive a range of doses, from 30 micrograms to 3.75 micrograms, without adjuvant -- that’s shown in brown -- or with adjuvant. That’s shown in green. I’m showing you with the horizontal reference line the CBER seroprotection

rate target. This is a plot of seroconversion rate, but because virtually all subjects were seronegative at baseline, the two parameters are interchangeable.

What you see is, first of all, that this is not a one-dose vaccine. Two doses are required, even with 30 micrograms. But the lowest dose included in this dose range easily surpassed the CBER acceptance criteria, which would be one of the considerations with respect to licensure.

The first study, the Phase I/II study, of Q-Pan H5N1 was designed to confirm the benefit of including AS03, its equivalence to D-Pan to link this development to that done with D-Pan, and to identify a dose that would be advanced into Phase III. This was a study that immunized 780 adults and was conducted at sites in the United States and Canada in 2007.

The control group is shown in purple. These subjects received unadjuvanted vaccine. The antigen concentration for all groups was 3.75 micrograms. What we varied, however, was the source of antigen and the formulation of AS03. AS03-A represents the full dose of AS03, as shown in the previous slides and as described by Dr. Collazo. But AS03-B represents half a dose. Green and blue are from Quebec. Orange and gold are from Dresden.

Adjuvant benefit was compared looking at Q-Pan

responses with adjuvant relative to without adjuvant. I'll describe the success criteria when we come to the study. We looked at immunogenicity equivalence between Q-Pan and D-Pan as well. If all of the Q-Pan groups had a seroprotection rate of at least 76 percent, then we planned to enroll contingency arms that would reduce the antigen dose by half and evaluate both formulations of AS03, A and B.

This study, in fact, confirmed AS03 benefit with respect to seroconversion rate increase. The success criterion was to show that it was greater than 15 percent. What we observed comparing the purple control group to the green candidate vaccine group was an increment in response of 80 percentage points.

It also confirmed the benefit of including AS03 by looking at the geometric mean titer increase that was afforded. The success criterion was greater than twofold, and what was observed as a 43-fold increase.

The same plot, geometric mean titer with a logarithmic scale. This shows the equivalent immunogenicity, with GMT ratios that approached 1 between Q-Pan and D-Pan.

Lastly, an observation that we made: There was virtually no anamnestic response with a second dose in those who received plain antigen, but there was a very

dramatic anamnestic response between dose 1 and dose 2 with the candidate vaccine.

We had to select a dose for advancement into Phase III. Phase III was intended to include subjects who were elderly, over the age of 65. We had no early development experience. We did a post hoc analysis. Fifty-five percent of subjects in this trial were under the age of 40, 45 percent were older. We age-stratified the population and then we looked at the four Q-Pan formulations that were tested. Green is the full dose of AS03, AS03-A, at 3.75 micrograms. Blue is 3.75 micrograms of antigen with a half dose of adjuvant. The gray and the white are the two contingency arms with half-antigen dose.

All of those responses in individuals under the age of 40 we believed were quite acceptable. But only the formulation of 3.75 micrograms with the AS03-A preserved the excellent geometric mean titer and seroprotection rate responses that were seen in younger individuals. The point is to compare the green bar on the right-hand side of the graph with the green bar that’s shaded on the left-hand side of the graph.

The other three formulations -- and these were limited sample sizes in these groups -- either had a decrease in geometric mean titer and/or a decrease in seroprotection rate. We felt that there would be even more

profound decrements in response that would be seen in elderly subjects, and so these formulations were set aside.

Here is the confirmatory immunogenicity and safety study that was done in a total vaccinated cohort of 4,561 subjects at 40 sites distributed across the United States and Canada, in 2008. This was an age-stratified enrollment. The bars in orange represent the candidate vaccine. The control in this case was saline placebo.

Individuals who were under the age of 50 were excluded unless they were healthy, because this was the population in which we intended to test manufacturing consistency. But individuals who were 50 and above were, in fact, in stable health. Subjects were excluded from the trial if they had an immunodeficiency condition, but otherwise were included, unless they had had a medication change or an adverse event within 30 days prior to their enrollment that would have been considered serious.

I’m showing you the lot-to-lot consistency ratio done. The other confirmatory objective in this trial was to show that seroconversion rate and seroprotection rate responses in the population 18 to 64 and 65 and above met the CBER acceptance criteria for immunogenicity using the HI test.

Here are the data that show consistent immunogenicity in three independent production lots of

antigen and of AS03.

Here is the response rate, both in terms of geometric mean titer and the seroconversion rate, labeled on the top of the vertical bars, for subjects under the age of 65, in blue, by the saline controls. Here are the elderly adults. Here is a subset analysis of the elderly adults, older than 75, with no noticeable decrement.

So the data that I have shown you establish that we have fulfilled the immunogenicity requirements for accelerated approval. Q-Pan H5N1, given 21 days apart, meets the CBER criteria in adults of all ages. Manufacturing consistency was demonstrated. The formulation we evaluated had a better immunogenicity profile than the currently licensed vaccine, acknowledging that these products were not studied concurrently.

Now I would like to share some clinical endpoint data from vaccines manufactured using the Quebec process, to support your discussion this afternoon of question 3.

Demonstration of clinical benefit due to administration of a split-virion antigen component of Q-Pan provides a minimum estimate of the efficacy that could be expected in an antigen-plus-adjuvant component vaccine. Q-QIV-006 evaluated vaccine efficacy of a quadrivalent seasonal vaccine, unadjuvanted, in children 3 to 8 years of age in eight countries in the Caribbean and Asia in the

2010-11 season. The control was hepatitis A vaccine, inactivated. Children were followed for 180 days following vaccination. The administration of vaccine was according to the recommendations articulated in 2010 by the ACIP.

The clinical endpoints that were evaluated were two:

• The standard approach, which we called any influenza, and all cases were confirmed by detection of influenza virus RNA by RT-PCR.

• We also characterized a subset of any influenza infections that we described as moderate to severe. This endpoint required a child to have one of the four manifestations listed on this slide. These cases represented about 40 percent of all cases seen in the control group. We believe that they represent the important clinical consequences of influenza disease in children.

Here are the data for efficacy: against the any-influenza endpoint, 55 percent, and against the moderate to severe endpoint, 73 percent.

Because we’re using this vaccine as a surrogate for protection against influenza A subtypes with pandemic potential, I want to show you the post hoc analysis that looks at type-specific protection using any influenza as the endpoint. You see that they are virtually identical.

That’s the antigen component of Q-Pan. What happens when you mix it with adjuvant? That can be determined if one performs a relative efficacy trial. That was done in the waning months of the 2009-2010 pandemic. Again in eight countries in Latin America and Asia, 6,000 children were randomized to receive either Q-Pan H1N1 twice -- and they received a pediatric dose, so that’s half the adult dose, or 1.9 micrograms of antigen with AS03-B -- or once, and that’s shown in orange, or they received an investigational formulation of H1N1 vaccine manufactured using the FluLaval process at 7.5 or 15 micrograms, depending on their age.

The relative efficacy means that you are looking at the incremental protection afforded by the inclusion of adjuvant.

This is a plot of disease-free survival over 385 days. The relative efficacy was 77 percent for two doses and 46 percent for one dose, although, because of the paucity of cases, the second estimate is not statistically confirmed. It includes a zero in the confidence interval.

In addition, I told you that 95 percent of the pandemic response in Canada was done using Arepanrix H1N1. There were three studies conducted by public health agencies in Canada that assessed field effectiveness. One study was submitted, because we had access to all of the

source data and could perform an independent analysis of those data. That was the study done in New Brunswick, which was in the same situation as the study in Maine. Vaccination was actually carried out almost simultaneously with the arrival of the first case. Within ten days of the onset of the pandemic, more than 60 percent of all children in the province had been immunized. There they saw 100 percent effectiveness.

Estimates in Manitoba and in a multi-province study in Canada also converged on this kind of estimate. These were not just children, but also adults of all ages. The range of effectiveness in these studies was 86 percent to 100 percent.

Let’s summarize what these clinical endpoint data support. Antigen-only had about 60 percent efficacy, 55 percent efficacy. Then there’s a relative efficacy of 77 percent, which can be translated into an absolute efficacy, if you look at this arithmetic expression. That translates into 90 percent efficacy in children, which matches the range of values observed with one-dose vaccination -- short-term protection -- in Canada.

GSK does propose that the 006 quadrivalent unadjuvanted vaccine study be the required study to confirm clinical benefit.

If this vaccine is deployed in the United States

in a pandemic situation, GSK, of course, will collaborate in government-sponsored studies of the vaccine safety and effectiveness. Observational studies can be feasible and reliable, but they need to meet the considerations that are shown on this slide. What I want the committee to consider is that in the US and in Canada, where this vaccine might be deployed, governments are better able than a sponsor to conduct these kinds of studies, because they control vaccine distribution, guide case assessments, and, most importantly, it’s their systems that capture vaccination status.

With that, I close my remarks and turn the podium over to my colleague, Dr. Felix Arellano, head of GSK vaccine safety and pharmacovigilance.

DR. ARELLANO: Thank you, Bruce.

It is a pleasure to be here to present the safety data for Q-Pan H5N1, which I will do following the outline shown in this slide. I will start with the nonclinical safety data. Then I will move to present the clinical trial safety data, an analysis of signals from H5N1 and H1N1, the pharmacovigilance plan for Q-Pan H5N1, relative benefit scenarios in a pandemic setting, and an assessment of safety and benefit-risk.

Just one slide to show the nonclinical safety data. The development program for the vaccine included

standard nonclinical toxicology studies, a total of 12, as shown in this slide, and two standard safety pharmacology studies of cardiorespiratory function in rats and dogs. The main finding was injection site inflammation, as would be expected with an adjuvanted vaccine. The nonclinical safety data then supported testing in humans.

I'm now going to present the clinical trial safety data using data from the pivotal trial 002. If you remember from Dr. Rainey's (phonetic) presentation, there were two pivotal trials, 001 and 002. 001 was much more of a short duration. The data from 002 can be extrapolated to 001.

002 included 4,561 subjects, with a randomization ratio of approximately 3 to 1. Two thousand six hundred six Q-Pan recipients and 870 placebo recipients were followed for 12 months. There were solicited local and general symptoms that were recorded for seven days after each dose, unsolicited adverse events through day 84, and medically attended adverse events and severe adverse events through day 364.

Moving now to the results, this slide shows the local reactogenicity, measured as pain, redness, and swelling, in orange for Q-Pan H5N1, in blue for placebo. The results show an increased incidence of local reactogenicity compared to placebo, but only for pain when

referring to grade 3.

Likewise, this slide shows general reactogenicity data, measured as arthralgia, fatigue, fever, headache, myalgia, shivering, and sweating, again in orange Q-Pan H5N1, in blue placebo. There was an increased incidence of general reactogenicity, but not grade 3 events in this care compared to placebo.

Concluding on 002, there was a greater frequency and intensity of reactogenicity for Q-Pan H5N1 compared to saline placebo. Lymphadenopathy, unsolicited adverse events, medically attended adverse events, severe adverse events, including fatal adverse events, and adverse events leading to withdrawal are discussed in the briefing book. I would just like to point out that there were similar frequencies observed between Q-Pan H5N1 and placebo.

I would now like to move to analyze an analysis of signals from H5N1 and H1N1 using data from the integrated safety summaries 1 and 2 and postmarketing data for H1N1.

This slide shows the main safety signals related to the GSK adjuvanted pandemic influenza program. By signals, we are using the CIOMS IV/VI definition, as shown in this slide. The left column shows the signal, the middle column, the source of the signal, and the right column, our assessment of each individual signal.

I’m going to be talking more in-depth about the potential immune-mediated diseases and narcolepsy, the two highlighted in orange. Moving down, autoimmune hepatitis will be discussed within the potential immune-mediated diseases. Anaphylaxis is a rare but well-described side effect of essentially all vaccines. Our assessment is that the risk of anaphylaxis for adjuvanted pandemic H1N1 vaccines is similar to that of other flu vaccines.

Guillain-Barre syndrome has been the subject of numerous epidemiological studies, both in adjuvanted and non-adjuvanted vaccines, with mixed results. Some of them show increased risk, some of them don't. The consensus seems to be that if there is a risk, the excess risk is between zero and 2 million cases per million persons vaccinated.

Solid organ transplant rejection is a signal undergoing investigation. The current data do not support a causal association. It should be taken into consideration that organ transplant recipients are at higher risk of developing influenza, and therefore get vaccinated more than the general population.

For these four signals that I am not describing in detail, if you have any questions, I will be happy to address them in the Q&A.

I’m now going to be moving to discuss pIMDs, or

potential immune-mediated diseases.

The source of the signal was a group of adverse events that together occurred more frequently among H5N1 recipients than control recipients. What we did to evaluate the signal was, first, to create a case series and perform a thorough medical review. Then we examined H1N1 clinical trial data, since H1N1 and H5N1 share some commonalities. Namely, they use the same adjuvant, and H1N1 was used and H5N1 will be used in the case of a pandemic. Then I will move on to review two external analyses that are not included in your briefing document, one an analysis of spontaneous reports from H1N1 vaccines, performed in EudraVigilance in the European Union, and a cohort study performed in Sweden.

The imbalance that I was referring to before was observed in what is called ISS-1. Just for clarification, ISS-1 included only H5N1 patients. ISS-2 included both H5N1 and H1N1.

The signal was a numerical imbalance for pIMDs in aggregate. These pIMDs were identified as 120 MedDRA preferred terms. This list was developed with input from external experts and CBER. The intention was to cast a net as wide as possible, acknowledging that it will be something that will yield high sensitivity, but low specificity.

ISS-2 included 11,376 D-Pan and Q-Pan H5N1 recipients. They were included in 28 adult clinical trials of Q-Pan and D-Pan both H5 and H1N1 vaccines. As I said, data from ISS-1 were included in ISS-2.

This net was cast then on ISS-2. This slide shows the 29 pIMDs observed with H5N1 in ISS-2. I would like to highlight three points here:

• One, I remind you about the three-to-one randomization ratio.

• Two, the scattering of the adverse events does not suggest a common pathophysiological pathway.

• Three, the small number of cases in each of these categories.

As written in the briefing document, for most of these cases, there were alternative explanations. I'm going to use an example in the following slide, for the three events that accounted for much for the imbalance.

The first one was the Bell's palsy/facial palsy/facial paresis/VII nerve paralysis group that had five patients. One of the diagnoses was then subsequently changed to stroke. Another event began eight hours after vaccination and had a negative rechallenge. The patient recovered after receiving a second dose.

There were three cases of psoriasis. One subject had psoriasis at study enrollment, and the investigator did

not think it had worsened after receiving vaccination. Another subject developed guttate psoriasis, which was attributed to a streptococcal infection by the investigator.

Polymyalgia rheumatica/temporal arteritis had four. One subject had symptoms prior to vaccination. The PMR symptomatology did not change. However, she did develop temporal arteritis after vaccination. Finally, another diagnosis of PMR was eventually changed to fever myalgia.

So the signal that was observed in aggregate did not seem to be confirmed in groups that had a common pathophysiological pathway.

I would like now to review briefly two studies. The first one is this one published by Isai et al., which was a EudraVigilance data and literature review, which essentially included all spontaneous reports reported to the European Union through EudraVigilance during the 2009-2010 pandemic for all H1N1 vaccines, both adjuvanted and non-adjuvanted. The reporting rates for autoimmune diseases are described in this slide. There were no differences in the reports of autoimmune diseases between adjuvanted and non-adjuvanted H1N1 vaccines, according to the authors.

The second is a retrospective cohort study

performed in Stockholm, Sweden, where almost 1 million persons unvaccinated were followed over eight to ten months. The authors define autoimmune diseases as being rheumatoid arthritis, diabetes, and inflammatory bowel disease, which are listed on this slide, highlighted in orange. There was no increased risk associated with vaccination for any of the three diseases.

In addition to that, the authors studied some other diseases that they referred to as neurological diseases. There was again no association between vaccination and multiple sclerosis and Guillain-Barre syndrome. They did report a small risk of Bell’s palsy that they attributed to several causes, including residual confounding.

Concluding on pIMDs: We believe that the currently available data from clinical trials, spontaneous reports, and an epidemiological study do not support a relationship between Q-Pan H5N1 and the induction of pIMDs. As will be discussed later during the pharmacovigilance plan, should the vaccine be used, GSK will continue to monitor reports of pIMDs.

I would like to move now to narcolepsy. We think it’s important to highlight the fact that the signal evaluation for narcolepsy was performed during widespread media attention in the European Union. During the pandemic

there was mass vaccination with GSK H1N1 vaccines in 47 countries. There was high coverage and/or exclusive use in several countries, including Finland, Sweden, and Canada.

Chronologically, in February of 2010, we received the first case. It was reported to authorities in a simplified PSUR. The monitoring of this disease was initiated.

Between April of 2010 and the end of May, first a second case and then two additional cases were reported. In July and August, Sweden reported a cluster of cases. GSK performed its first analysis, and EMA mandated an investigation.

At the same time, around August of 2010, the MPA, the Swedish regulatory authorities, issued a press release on narcolepsy, and widespread media attention began in the European Union. It is important to understand that the whole evaluation of the signal in the European Union was actually done under widespread media attention.

Just one slide on the background of narcolepsy. Narcolepsy is a very rare disease. The background incidence reported by the VAESCO consortium is around 10 per million person-years, and it’s even lower in children, between 1 and 5 per million person-years. It is difficult to diagnose and validate. It is characterized by excessive daytime sleepiness and sleep paralysis, frequently

associated with cataplexy.

Its diagnosis requires access to a sleep clinic. Decreased levels of hypocretin-1 in cerebrospinal fluid is considered pathognomonic.

The etiology and pathophysiology of narcolepsy are poorly understood. The presence of an HLA DQB1 0602 allele is considered a necessary condition. It is present in between 15 and 25 percent of the population, more prevalent in Northern Europe than in Southern Europe. Not everybody with the allele develops the disease. There are several factors that have been postulated as able to trigger the development of the disease, among them streptococcal infections, influenza, including H1N1, infection. As I said before, the pathophysiology is unknown or poorly understood, and some authors have postulated a possible autoimmune mechanism.

Just one slide with some exposure data. In clinical trials of H5 and H1N1, with almost 23,000 subjects, there were no reports, which is to be expected, given the low background incidence of the disease. For Q-Pan H1N1, also known as Pandemrix, there were 58.5 million vaccinated, with over 100,000 pregnant women and 2.8 million children. For D-Pan H1N1, also known as Pandemrix, there were 31 million vaccinated, with almost 195,000 pregnant women and 6.7 million children.

Given the variety of this condition, it is logical that the follow-up of the signal had to be done through epidemiological studies. I'm first going to present data for Q-Pan H1N1 on a study in Quebec. I apologize for not having included this in the briefing document, but we literally just got permission from the author to present these data, which are preliminary results. I would like to highlight three points.

One of them is that the authors reported that they had difficulty finding cases of narcolepsy, which I think is a finding in itself. Secondly, the incidence rate reported, 1.3 per million, is in the ballpark of what has been previously reported. The age- and gender-adjusted risk ratio, which was 1.06, with 95 percent confidence intervals, suggested no association between the use of Q-Pan H1N1 and narcolepsy in Quebec.

On the other hand, in Europe there have been studies, in Finland, in Sweden, in Ireland, and in France that have showed increased risk associated with the use of D-Pan H1N1 and narcolepsy. The relative risk ranged between 5 and 13, and the attributable risk between 3.6 and 6.

I would like to concentrate a little bit more on the VAESCO study, which is listed on the upper part of the slide.

The reason that I want to highlight the VAESCO study is, first, it was commissioned by the European CDC. It’s a large-scale, multinational, case-control study, which has a standardized methodology, meaning that the individual studies performed in individual countries were using similar methodologies. It also attempted to consider controlling for biases and confounding.

The results show, for the signaling countries, which were predefined -- Sweden and Finland, shown to the right -- an increased risk of narcolepsy, with a pooled analysis of 14.2. On the other hand, for Norway, France, Denmark, Holland, and the United Kingdom, there was no association in children. The point estimate was an order of magnitude lower and the 95 percent confidence intervals included the 1.

It is important to take into consideration when reviewing these results that these studies have some limitations. One of them -- the H1N1 infection has been postulated as one of the factors that can trigger the development of the disease. In all these studies there was close temporal proximity between the H1N1 peak of infection and vaccination, which potentially confounded the results.

There were also important potential referral and ascertainment/recall biases, which were not fully accounted for in most studies, although it has to be acknowledged

that the VAESCO study did attempt to do so.

Likewise, there was a lack of adjustment for potential confounders, such as comorbidities. Again, the VAESCO authors tried to do so.

Finally, the Swedish studies included spontaneous reports as cases, which will bias the results towards an association with the vaccine.

I would like to clarify that the fact that we do not believe that the signal is confirmed doesn’t mean that we don't take this very seriously. We do. We have an ongoing set of research activities that can be divided into three major groups: epidemiological, nonclinical, and animal studies. This research plan has been developed after expert consultation, agreed to by regulatory authorities -- namely, the European Medicines Agency -- and will be conducted in collaboration with experts in the field.

Summarizing on narcolepsy: To date, there is no signal with Q-Pan H5N1, which is why we’re here. To date, there’s no signal with Q-Pan H1N1. There is a signal with D-Pan H1N1, based on observational data, which can be deemed as inconclusive. It is our position that the currently available data are insufficient to determine whether there is a causal relationship between D-Pan H1N1 and narcolepsy. Further research is necessary, which is

why we have the extensive program under way.

I would like now to move back to Q-Pan H5N1 and present the pharmacovigilance plan for the vaccine.

The PVP, the pharmacovigilance plan, includes general -- meaning common for all pandemic flu vaccines -- and some specific-to-Q-Pan-H5N1 activities. The specific activities will depend upon circumstances of use of the vaccine, whether it's going to be used in a civilian or military population, in a pandemic or in a pre-pandemic setting.

As written in the briefing document, the pharmacovigilance plan that will be proposed for the US is based on the pharmacovigilance plan that has been agreed with the European Medicines Agency. These activities that I’m going to describe in the next few slides have yet to be agreed upon with CBER.

I would like to highlight that we will need to rely on US agencies for near-real-time analysis of adverse events in data systems, since these are not available to sponsors.

The following activities will be contingent on the feasibility at the time of vaccine use. We will establish a US pregnancy registry, as is normally done for seasonal flu vaccine. Also as we routinely do, we will determine background incidence rate in the United States

for adverse events of special interest and other adverse events following vaccination, to perform observed versus expected. To do that, we will get data from US claims databases.

We will conduct a prospective cohort study. I would like to clarify that in the briefing document it says that it will be done in the European Union. We will do it wherever the vaccine is available, North America or Europe.

Finally, we will continue to work with sleep experts and professional societies to establish sentinel networks for early detection and validation of narcolepsy cases.

With this, I want to move to talk about the relative benefit scenarios in a pandemic setting.

As has been explained by other presenters, there has been continuous transmission during the last ten years of H5N1 virus from birds to animals. WHO has accounted for 608 cases, with 359 deaths, with an overall case fatality ratio of 59 percent. Nobody knows whether there's going to be an H5N1 pandemic or when it will be, but some of the projected social consequences of such a pandemic can only be qualified as "sobering." In the US, there are estimates of between 25 and 50 percent of the population becoming ill, with projected excess deaths of up to 2 million, worldwide, 25 percent to 50 percent of people becoming ill,

and excess deaths between 16 million and 160 million.

What we have attempted to do here is to try to explore the relative benefit of H5N1 vaccines on mortality using three parameters that I'm showing here:

• Vaccine effectiveness both for adjuvanted and non-adjuvanted vaccines. For adjuvanted vaccine, we have taken this from D-Pan H1N1 effectiveness studies. We have used a range of numbers between .62 and .97. For the non-adjuvanted vaccines, we have inferred this from immunogenicity data published by Treanor et al., and used figures between .3 and .57.

• The second parameter is attack rate as a surrogate of infectivity. We have taken data from past pandemics and used numbers between .14 and .40.

• Finally, case fatality ratio as a surrogate of mortality, again data used from past pandemics, with figures between 1 and 5 percent.

There is a total of 54 possible combinations that you can put in scenarios. We are showing here what we call best, most realistic, and worst. By best, we mean best from a societal or a patient point of view. In other words, best would be a situation where one would have a high vaccine effectiveness and a mild pandemic, with low attack rate and low case fatality ratio. Worst would be the opposite. It will have low vaccine effectiveness, with

high attack rate and high case fatality ratio. By most realistic, we mean our best guess as to what we think a real pandemic may look like.

The two columns to the right that are highlighted in orange show the number of prevented deaths by the use of adjuvanted and non-adjuvanted vaccines per 100,000 persons vaccinated. I'm going to show data in a graphic later. What this graphic shows is that the adjuvanted vaccine would prevent approximately twice as many deaths as non-adjuvanted vaccines, regardless of the scenario, and that the worse the pandemic would end up being, the higher the absolute number of deaths prevented.

Finally, I'm going to give an assessment of safety and benefit-risk.

We believe that the Q-Pan H5N1 safety profile supports licensure for the proposed indication. The only confirmed signal from the development program is an increased incidence of reactogenicity, both general and local, compared to placebo. We believe that the benefit-risk balance of Q-Pan H5N1 is positive, especially in the context of a pandemic. We have a robust pharmacovigilance plan that is built upon experience with the H1N1 pandemic and will allow us to monitor the safety of Q-Pan H5N1, should it be used.

With this, I want to thank you for your

attention. I'll pass the podium to Donna Boyce.

MS. BOYCE: Thank you, Dr. Arellano.

In conclusion, the accelerated approval licensure criteria have been met, based on the acceptable safety and immunogenicity data from the two pivotal studies, 001 and 002. In accordance with the regulations, GSK proposes that Q-QIV-006 be the required post-licensure study to verify clinical benefit of Q-Pan H5N1. The results of Q-QIV-006 have been submitted to CBER, and traditional approval is anticipated in 2013. GSK expects to work with the US government to collect safety and effectiveness data when Q-Pan H5N1 is used.

Regarding the benefit-risk, the Q-Pan H5N1 immunogenicity and safety profile supports licensure for the proposed indication. The addition of the AS03 adjuvant system to the vaccine results in high immunogenicity and is antigen sparing. In the context of a pandemic or increased risk, the benefit-risk is positive. Moreover, GSK's experience with the H1N1 pandemic will allow GSK to more effectively monitor the safety of Q-Pan H5N1 through the pharmacovigilance plan.

Finally, licensure of Q-Pan H5N1 will improve pandemic preparedness. It offers the US government a more immunogenic alternative to the currently licensed H5N1 vaccine, and it establishes the necessary regulatory

platform to enable rapid licensure of a pandemic strain-specific vaccine via the strain-change supplement. Once licensed, the antigen-sparing property of Q-Pan H5N1 will increase the number of doses available for distribution in the US. Therefore, this vaccine is expected to provide a significant public health benefit in the event of an H5N1 pandemic.

That concludes our presentation.

DR. DAUM: Thank you. Let me begin by applauding GSK for being on time and getting us back on schedule.

I would like to ask the committee members now for clarifying questions on the sponsor's presentation. There are many issues that I'm sure we will want to return to this afternoon, but right now we'll ask for clarifying questions or comments, if any. Dr. Tacket.

DR. TACKET: Could you comment on the biologic plausibility of narcolepsy as an issue to the vaccine, to help us evaluate how likely that is to be caused by the vaccine?

DR. ARELLANO: If I understood your question, you're asking whether I can comment on the biological possibility of narcolepsy --

DR. TACKET: (Off-mic)

DR. ARELLANO: Unfortunately, the problem is that the pathogenesis of narcolepsy is really poorly understood

or unknown. It’s almost impossible to speculate how the vaccine may actually have contributed to it. I really don't know.

Maybe in the afternoon session we can bring something up.

DR. DAUM: Dr. Bennink.

DR. BENNINK: Along the same line, is part of the going with the Q versus the D related to any of this?

DR. ARELLANO: No.

DR. BENNINK: So you aren’t looking at any differences there. If you wanted later to make something at the Dresden facility, would you make it with the -- does that have any relationship on the approvals or anything else, at a later date?

DR. ARELLANO: If you allow me, I’m going to divide your question into little pieces. The first thing that I would like to highlight is the fact that it is always tempting to dichotomize signal with D and no signal with Q. I think it’s important to remember that so far the signal with D has not been confirmed.

In addition to that, if there was something related to the manufacturing, we would have expected that with the Dresden manufacturing of trivalent vaccines, of which 50 million doses have been distributed in the US, we should have seen some cases of narcolepsy, and we haven’t.

The other part of the question, I think, was related to whether that had anything to do with the decision to go with Q or D. It didn’t.

DR. DAUM: Dr. McInnes.

DR. MCINNES: I have a question. Please just go over again the choice of the higher concentration of adjuvant. Those slides went by really quickly. I think it starts on 21 and goes about five slides. I would like to understand how many vaccinations -- it’s not on the slide, and I can’t tell.

DR. INNIS: This is the post hoc analysis that was done. You remember that we set aside responses in the younger-age adults, because they don't discriminate differences. So we’re going to focus on what was seen in the 41-to-64-year-old individuals. There are geometric mean titers and labeled seroprotection rates 21 days following a second dose. What we concluded was that the formulation in green, 3.75 micrograms with AS03-A, was the only formulation that preserved the geometric mean titer response and the seroprotection rate that was observed in younger adults. The other three formulations had a decrement in one or both of those parameters that we predicted would be even more decreased in elderly individuals or in any adult with underlying medical conditions, and therefore we would not be able to attain

the CBER immunogenicity criteria that were offered as guidance for accelerated approval.

I think the other consideration was that the difference in reactogenicity between AS03-A and AS03-B in the entire adult population of 18 to 64 -- there really was marginal benefit in reducing the adjuvant content. It was not a good tradeoff for less immunogenicity.

The last consideration in selecting this dose was that this was a vaccine to be stockpiled and potentially deployed, even though the antigen matching may not be perfect, because these kinds of vaccines -- a strain-matched vaccine would not be available for several months. These are homologous immune responses. This is the optimal immune response. When you look at heterologous responses, moving away from AS03-A is very detrimental.

DR. DAUM: Thank you. Dr. Bennink.

DR. BENNINK: Just one more on the adjuvant. Did you ever consider doing a non-adjuvanted second dose?

DR. INNIS: Could I have slide Q-Pan 10?

We never directly did that study. However, we took veterans of the 001 study, who received two-dose priming, and 15 months later, we gave them a dose of a A/Turkey with or without adjuvant.

If you look at the right-hand side of this plot -- first, look at the second bar. The second bar from

the left is two-dose priming with the candidate vaccine and boosting with 3.75 micrograms with AS03. That's the comparator response in the prime/boost situation. If you look at the bar on the extreme right, that's two doses of plain antigen. So it can be effective, but it doesn't have the same kind of response.

DR. DAUM: People look at little perplexed at that last slide. Ed, do you want to comment?

DR. MARCUSE: I would like to just see it a little longer, if I could, that last slide.

DR. INNIS: Is there another question?

DR. DAUM: I think we wanted to contemplate the slide for another minute or two. We're a little slow.

DR. INNIS: We've been contemplating it for weeks.

DR. DAUM: Is the committee content or are there comments?

DR. INNIS: I would tell the committee that we have only shown you homologous immune responses. We have data on heterologous responses, on neutralizing responses, on CMI, on prime/boost, on duration. If you want to get into these parameters, there are data, and we can share them with you this afternoon.

DR. DAUM: We may return to it this afternoon. Right now we're looking for clarifying questions on things

that were said this morning that the committee doesn't understand.

Dr. Bennink.

DR. BENNINK: Just one more thing. On the solid tumor data, what were the numbers of people that had the transplantation?

DR. INNIS: Solid organ transplantation.

DR. BENNINK: Yes, solid organ transplantation. What were the numbers that were vaccinated versus the numbers that actually had an issue of rejection.

DR. ARELLANO: Twenty-three in our safety database.

But I didn't really quite get the question, sorry.

DR. BENNINK: Just the number of people that were vaccinated that had had transplantation and then the number of those that had rejections.

DR. ARELLANO: Do you mean in clinical trials?

DR. BENNINK: Yes.

DR. ARELLANO: There were none included in clinical trials. The data that we showed were from different epidemiological studies.

DR. DAUM: One more question. Dr. Gellin.

DR. GELLIN: This is for the stockpile. The company has no plans to market this. Are you doing that

same thing or anything different in other countries?

MS. BOYCE: Could you repeat the question?

DR. GELLIN: This is for the US stockpile, with no plans to market this separately. Then the question is, how are you doing this in other countries with similar products?

MS. BOYCE: In the same manner.

DR. GELLIN: All will be government stockpiles for government distribution.

MS. BOYCE: That’s correct.

DR. DAUM: There are no plans to market this anywhere in the world.

MS. BOYCE: No. It’s going to be distributed via government.

DR. DAUM: Thank you.

DR. GELLIN: And then a very different question. At several points in your slides, you talked about the benefit-risk being positive. Tell us about how you would think about -- how would you get to a benefit-risk being neutral?

DR. ARELLANO: Your question was, how would we get to a negative benefit-risk of the vaccine?

DR. GELLIN: Neutral. Considerations that go into that. Where’s the inflection point when it goes from positive to neutral, to negative?

DR. ARELLANO: The relative benefit scenarios that I was showing refer only to mortality. For me, it would actually be complicated to -- obviously, if vaccine would not have an effect on mortality and would be associated with a side effect that would be serious, there probably would be a moment where those two things would balance.

If I can have the slide up, please.

Just to put this into context, if you're thinking about narcolepsy, just think about the fact that the worst excess risk associated with narcolepsy so far has been in the Finnish study. Let's assume that that risk, which was seen only in children, could be extrapolated to the adult population, which is what we're talking about here. We're talking about an excess risk of 6 per 100,000. If you want to use the most likely case or even the best case, you are talking about 800 deaths versus six cases of narcolepsy, or 150, 180 deaths versus a case of narcolepsy.

So the only moment when I would actually conceive a balanced benefit-risk would be if the vaccine would not have an effect of preventing death, without even taking into consideration morbidity, pneumonia, et cetera.

DR. DAUM: Okay, I think we're questioned out for now. I know there are many topics we'll want to come back to this afternoon, but for now we're going to hear the FDA

presentation and call on Dr. Andrea James for that.

Welcome, Dr. James. Good morning. We are running ten minutes behind schedule.

DR. JAMES: I'm going to try to talk very quickly.

DR. DAUM: Not too quickly. We want to hear what you have to say.

DR. JAMES: I'll try to talk at the appropriate pace, but I understand that I am standing between all of you and lunch.

DR. DAUM: That's okay. You're standing between all of us and our discussion as well. That's important.

Agenda Item: FDA Presentation

DR. JAMES: Good morning again. My name is Andrea James. I'm a clinical reviewer in the Division of Vaccines in CBER.

This morning I'm going to be presenting the clinical review of data supporting the immunogenicity, safety, and effectiveness of influenza A H5N1 virus monovalent vaccine, adjuvanted.

I will begin by highlighting a few things about the product. I will go on to discuss the two pivotal studies submitted in support of the licensing application, Q-Pan-001 and Q-Pan-002, focusing at first on immunogenicity. I will digress from the pivotal studies

momentarily to briefly discuss the Arepanrix Q-Pan H1N1 effectiveness study submitted in support of Q-Pan H5N1. I will then return to the pivotal studies to discuss safety results from those studies, followed by a presentation of a number of additional safety evaluations conducted by GSK, including surveillance for adverse events of special interest and potentially immune-mediated diseases, the results of two integrated safety summaries, postmarketing safety of related AS03 adjuvanted pandemic H1N1 products, and lastly, GSK's proposal for their postmarketing pharmacovigilance plan.

Finally, I will wrap up by presenting the questions that we would like the committee to vote on or discuss after lunch.

Influenza A H5N1 virus monovalent vaccine, adjuvanted, is GSK's candidate monovalent pandemic influenza vaccine, manufactured in Quebec, Canada, using the licensed FluLaval process.

The proper name, which is the only name -- you just heard me say it, and it's a mouthful -- is influenza A H5N1 virus monovalent vaccine, adjuvanted. GSK did not propose a trade name. You heard earlier Dr. Collazo talk about our naming convention. I will try very hard throughout my presentation to refer to it as Q-Pan H5N1. I may slip sometimes and call it Q-Pan, but I mean Q-Pan

H5N1. For my discussion, you can assume that if I say Q-Pan H5N1, that also includes the AS03-A or the full dose of adjuvant. I will try to differentiate if I am talking about a different formulation of the adjuvant.

As you have already heard, it’s an inactivated split-virion A/H5N1 influenza virus antigen mixed with AS03 adjuvant, which is an oil-in-water emulsion adjuvant containing squalene, an unsaturated metabolizable oil extracted from shark liver, D,L-alpha-tocopherol, which is vitamin E, and polysorbate 80. AS03 is thought to enhance both the innate and the adaptive immune responses by enhancing delivery of antigen to antigen-presenting cells.

The proposed indication for Q-Pan H5N1 is for the prevention of disease in persons 18 years of age and older at increased risk of exposure to influenza A virus/H5N1 subtype contained in the vaccine.

The proposed dosage is 3.75 micrograms of H5N1 HA, plus AS03. Antigen dose was assessed in the study D-Pan-H5N1-007. I think we heard Dr. Innis talk about this study. The study was D-Pan again, Dresden-manufactured pandemic vaccine. That’s GSK’s other pandemic vaccine. In the study they used an A/Vietnam H5N1 strain, and a range of antigen doses were studied, ranging from 3.75 micrograms up to 30 micrograms, with and without AS03-A.

The results were that the hemagglutinin-

inhibiting antibody responses were low in an antigen dose-dependent fashion when no AS03 was added, but high in an antigen dose-independent fashion when AS03 was present.

The results of this study led GSK to select the lowest antigen dose of 3.75 micrograms to move forward with in their clinical development.

You have already heard about the vaccine presentation and the proposed administration, so I will skip those slides and move directly into the pivotal studies of Q-Pan H5N1, 001 and 002, which I will from here on out refer to as 001 and 002.

Both studies had a number of common trial elements:

• They were both conducted at multiple sites in the US and Canada.

• They were both randomized, controlled, single-observer-blind studies.

• They both evaluated immunogenicity and safety.

• In both trials vaccine and control were administered on days 0 and 21.

• In both trials the Q-Pan active test arms received the strain A/Indonesia/5/2005.

• Both trials enrolled healthy adult males and females who had no prior history of H5N1 vaccination.

Study 001 was a Phase I/II study. It was

conducted in ten US and Canada sites. It enrolled adults 18 to 64 years old. The active control in that study was unadjuvanted H5N1, 3.75 micrograms of HA.

The study objectives were to demonstrate adjuvant activity by comparing Q-Pan H5N1 adjuvanted with AS03 A, or full-dose adjuvant, and AS03-B, or half-dose adjuvant, versus unadjuvanted H5N1 vaccine. Other objectives were to demonstrate the safety of Q-Pan H5N1 versus unadjuvanted H5N1 vaccine and to demonstrate the immunologic equivalence of Q-Pan H5N1 versus D-Pan H5N1.

I think in Dr. Innis' slides, he said 780, but, in fact, this study enrolled 680 subjects. Hopefully that will help us skip a clarifying question after my talk. It enrolled them in a 1:2:2:2:2 fashion to unadjuvanted H5N1 vaccine or to Q-Pan or D-Pan with AS03-A, again, full-dose adjuvant, or AS03-B, half-dose adjuvant.

The mean age of subjects in this study was 38.6 years, with slightly more subjects being 18 to 40 years old. There were slightly more women enrolled in this study. The majority of subjects were Caucasian. You can see here that the majority of subjects received two doses of vaccine and completed the study through day 42 and then again through day 82. Of note, no subjects withdrew due to an AE.

The immunogenicity evaluations occurred on days

0, 21, 42, and 182, and the primary endpoint was vaccine-homologous virus antibody response in subjects receiving two doses of study vaccine, as demonstrated by the HI antibody titer at day 42. Secondary endpoints included HI antibody response after a single dose of vaccine and persistence of HI antibody response six months post-dose 1.

Immunogenicity success criteria for 001 were based on demonstrating the activity of the AS03 adjuvant and stated that the adjuvant activity would be supported if on day 42, after two doses of study vaccine, the lower bound of the 95 percent confidence interval of the difference in Q-Pan H5N1 minus unadjuvanted H5N1 seroconversion rates was greater than 15 percent and the lower bound of the 95 percent confidence intervals around the geometric mean titer ratio, Q-Pan H5N1 over unadjuvanted H5N1, was greater than 2.

The primary immunogenicity analysis population was according-to-protocol cohort for analysis of immunogenicity, or the ATPI population, which included subjects who met all eligibility criteria, complied with protocol procedures, met no elimination criteria, provided a complete set of immunogenicity endpoint measures at day 0 and day 42, and received the correct vaccine.

You can see on this slide that the primary outcomes for immunogenicity were met, demonstrating the

activity of AS03, with the lower bound of the 95 percent confidence interval around the seroconversion rates equaling 69.4, well above the prespecified difference of greater than 15, and the lower bound of the 95 percent confidence interval around the GMT ratio equaling 29.9, well above the prespecified lower bound of greater than 2.

In this slide I present the secondary HI immunogenicity results, which show seroconversion rates, percent of subjects with HI titers greater than or equal to 1 to 40, and GMTs at days 21, 42, and 182. At all time points, the adjuvant effect is noted, with the maximum effect occurring at the day 42 time point.

As you have heard, GSK performed a post hoc immunogenicity analysis evaluating the adjuvant effect of AS03-A as compared to AS03-B by age strata, and they found that AS03-B performed less well in the older cohort, having lower GMTs as compared to AS03-A. These findings supported GSK’s decision to move forward with AS03-A as the to-be-marketed adjuvant formulation in the adult population.

In conclusion, the immunogenicity data from 001 supported the selected antigen dose of 3.75 micrograms, the selected adjuvant dose of AS03-A, and the need for two doses of vaccine to produce an adequate -- and when I say adequate here, I mean meeting CBER’s suggested immunogenicity criteria -- HI antibody response.

Moving on to study 002, it was a Phase III study conducted at 40 US and Canada sites, enrolling adults greater than or equal to 18 years. The control in this study was saline placebo. The immunogenicity evaluations again were conducted on days 0, 21, 42, and 182.

A total of 4,561 subjects were enrolled and stratified by age, 18 to 64 and greater than 64 years. Randomization was 3-to-1, with 3,422 subjects being enrolled in the Q-Pan H5N1 arm and 1,139 subjects being enrolled in the saline placebo arm. There was an immunogenicity subset of approximately 2,000 subjects and a lot-consistency subset of approximately 1,200 subjects.

The objectives of 002 were:

• To demonstrate an immune response that met CBER's suggested immunogenicity criteria to support accelerated approval of a pandemic influenza vaccine.

• To demonstrate lot consistency for three antigen and three adjuvant lots.

• To demonstrate the safety of Q-Pan versus saline placebo.

At this point, I would like to say that lot consistency was met, and I'm not going to refer to lot consistency any more during this presentation.

The mean age of subjects was 39 years for the younger cohort and 72 years for the older cohort. Again we

see slightly more women enrolled in this study, and again the study population was predominantly Caucasian, with 86 percent in the younger cohort and 94 percent in the older cohort.

The majority of subjects received two doses of vaccine and completed the study through day 42 and day 182. You can see on this slide that only 76 percent of subjects completed the study through day 364. But it’s important to note that this day 364 safety evaluation was an amendment to the original study protocol, and so subjects had to be reconsented for this evaluation.

The primary immunogenicity endpoints were established on day 42, 21 days post-dose 2, and were vaccine-homologous virus HI seroconversion rates, proportion of subjects with vaccine-homologous virus HI reciprocal titers greater than or equal to 40, and the GMT ratio of vaccine-homologous virus reciprocal HI titers with two-sided 95 percent confidence intervals within 0.67 to 1.5 for lot consistency.

I fibbed a little bit. I did bring up lot consistency again. But that was just for the endpoint.

Secondary endpoints included persistence of HI antibody response through six months post-dose 1, as we saw in 001.

The study was powered to determine whether, 21

days after two doses of Q-Pan H5N1, the measured post-immunization vaccine-homologous virus HI titers met CBER's suggested criteria for clinical data needed to support accelerated approval of a pandemic influenza vaccine, as set forth in our 2007 guidance. As you can see in this table, the guidance suggests that post-vaccination the lower bound of the 95 percent confidence interval of the proportion of subjects achieving seroconversion should be at least 40 percent in the younger age cohort and at least 30 percent in the older age cohort, and that the lower bound of the 95 percent confidence interval of the proportion of subjects achieving HI antibody titer greater than or equal to 1 to 40 should be at least 70 percent in the younger age cohort and at least 60 percent in the older age cohort.

It's important to note that these criteria and the 1-to-40 HI antibody titers are borrowed from seasonal influenza. Historical data suggests that at a titer of 1 to 40, approximately 50 percent of subjects may be protected from illness due to seasonal influenza virus.

You can see on this slide that the primary immunogenicity endpoints in 002 were met. On day 42, the proportion of subjects who seroconverted after two doses of Q-Pan exceeded CBER's suggested lower bound of 40 percent for the young age cohort and 30 percent for the older age

cohort. Similarly, subjects exceeded the suggested lower bound of 70 percent for proportion of subjects achieving an HI titer of at least 1 to 40 in the younger cohort and 60 percent in the older cohort.

GMTs were not part of the primary immunogenicity outcomes, outside of lot consistency, but I have included them here for your reference.

You can see on this slide that the day 182 data shows a decrease in seroconversion rates and proportions maintaining HI titers of at least 1 to 40 from day 42. However, the seroconversion rates and HI titers greater than or equal to 40 were still noted in greater than 60 percent of subjects in both age cohorts, with lower bounds in the mid-50 percent range.

In summary, Q-Pan H5N1 vaccine demonstrated the ability to antigen dose-spare down to 3.75 micrograms, yet still achieve an adequate HI antibody response, as defined by CBER’s suggested immunogenicity criteria, after two doses of vaccine.

This is where I will digress momentarily from the pivotal studies to discuss the Arepanrix Q-Pan H1 effectiveness study submitted as a possible confirmatory study from which to infer Q-Pan H5N1 effectiveness.

Very briefly, Dr. Van Buynder et al. conducted a test-negative case-control study to evaluate the

effectiveness of Arepanrix, GSK's adjuvanted H1N1 pandemic vaccine, in children 6 months to less than 10 years of age during the 2009-2010 H1N1 pandemic. The study was sponsored by the New Brunswick Department of Health Canada.

It's important to note that GSK did not participate in the study conduct. CBER did not provide input into the study design. Safety data were not collected during the study. Arepanrix was evaluated at a single 0.25-mL dose, which consisted of 1.9 micrograms of H1N1 HA plus the half-dose adjuvant, AS03-B.

On to the study population. Of the approximately 73,000 children age 6 months to 9 years in New Brunswick, 116, or 0.16 percent, of the total population were tested for H1N1, which meant that only 116 children were eligible for study enrollment. Of those 116 children, 91 children met study criteria and agreed to participate. Of those 91, 28 were RT-PCR-confirmed H1N1-positive by nasal swab, and so considered cases. The other 63 were RT-PCR-negative for H1N1 and were considered controls.

Looking at the results: When subjects were vaccinated at least 14 days prior to symptom onset, the estimated vaccine effectiveness was reported at 100 percent, with a lower bound of 79.5 percent. When subjects were vaccinated at least ten days prior to symptom onset, the estimated vaccine effectiveness was reported at 96

percent, with a lower bound of 66 percent.

However, these estimates of vaccine effectiveness have to be viewed cautiously, given a number of study limitations, including very small sample size, a large percentage of subjects who were excluded from the effectiveness analysis, the potential for bias in the study, and the retrospective design of the study.

In conclusion, the Arepanrix effectiveness study conducted during the 2009-2010 H1N1 pandemic suggests that a single 0.25-mL dose of Arepanrix H1N1 was effective against H1N1 influenza virus in this small study in children. However, given the limitations that I cited above, CBER is unable to use the results of this study to confirm the effectiveness of Q-Pan H5N1.

Now I will go back to the pivotal studies, 001 and 002, and discuss the safety results.

The primary safety population was the total vaccinated cohort. These included subjects who received at least one dose of vaccine, had any post-vaccination data, and it was based on treatment actually received.

Safety evaluations included diary card solicited reactogenicity events on days 0 through 6, unsolicited adverse events on days 0 through 84, medically attended and serious adverse events, in 001, on days 0 through 182, and medically attended and serious adverse events, in 002, on

days 0 through 364.

The AE grading scale used for most of the solicited events ranged from mild to severe, mild being no interference with normal activities, moderate being some interference with normal activities, and severe preventing normal activity. Redness and swelling were measured events, with grade 3 being greater than 100 millimeters.

When we look at local reaction by subject for dose 1 or dose 2 -- because the frequency and severity were similar regardless of the dose -- you see that pain was the most common solicited local event, experienced by both treatment groups. However, nearly four times as many Q-Pan H5N1 subjects experienced pain as compared to the unadjuvanted H5N1 vaccine subjects. Although grade 3 severe pain was not common -- we usually define common as occurring in greater than 10 percent of subjects -- it did occur in approximately 6 percent of Q-Pan H5N1 subjects compared to only 1 percent of unadjuvanted H5N1 subjects.

You can see that any-grade redness and swelling occurred to a much lesser degree and only occurred in the Q-Pan H5N1 arm.

On this slide you see that myalgias occurred in nearly 50 percent of the Q-Pan subjects, which is two and a half times more subjects than in the unadjuvanted H5N1 arm. Headaches and fatigue were a close second and third

frequency events, and arthralgias occurred in a significantly higher proportion of Q-Pan H5N1 subjects as compared to the unadjuvanted H5N1 subjects. Also you can see that more subjects experienced grade 3 severe myalgias, headaches, and arthralgias in the Q-Pan H5N1 group as compared to the unadjuvanted H5N1 group.

Sweating and shivering were also commonly reported by Q-Pan H5N1 subjects. You can see that it was reported by approximately two times as many subjects as in the unadjuvanted H5N1 group. Again, here the results were similar post-dose 1 and dose 2 for both treatment groups.

More Q-Pan H5N1 subjects required antipyretics in the seven-day post-vaccination period than the unadjuvanted H5N1 subjects. However, fortunately for the Q-Pan H5N1 subjects, the events resolved in a median of three days and did not require any medical attention.

When looking at unsolicited adverse events, we see that slightly more Q-Pan subjects reported unsolicited adverse events than the unadjuvanted H5N1 subjects. We need to keep in mind that the 001 database is fairly small. But when drilling down and looking closely at the unsolicited events, we see that 2 to 3 percent of subjects -- which literally translates into three to five subjects -- in the Q-Pan H5N1 arm exclusively experienced the unsolicited events of diarrhea, anemia,

lymphadenopathy, dizziness, muscle spasms, and sinusitis, which may account for the slight imbalance that we see between the adjuvanted and the unadjuvanted arms with respect to reporting of unsolicited AEs.

With regard to medically attended adverse events, they were actually reported by more unadjuvanted H5N1 subjects than Q-Pan H5N1 subjects.

SAEs through day 182: There were three SAEs in two Q-Pan H5N1 subjects. One subject had cholelithiasis and pancreatitis and another subject had chest pain. All these AEs were deemed vaccine-unrelated by the investigator, and based on the information that I reviewed, appear to be unrelated. No deaths were reported in 001.

Moving on to 002, and looking at local reactogenicity, it looks very similar to 001. You see that pain is the most common event, occurring in 83.2 percent of the Q-Pan subjects versus 20 percent of the saline placebo subjects. You can see that more than a third of subjects experienced activity-limiting, moderate-grade pain, and nearly 5 percent experienced severe pain. Between 9 and 10 percent of subjects experienced redness and swelling.

When we look at the systemic reactions, we see that myalgias and arthralgias occurred in more than twice as many Q-Pan H5N1 subjects as compared to the placebo subjects, and fatigue occurred in approximately one and a

half times as many subjects.

The remainder of the systemic reactogenicity events were all experienced by slightly more Q-Pan H5N1 subjects than placebo subjects. However, unlike in 001, grade 3 events were not reported by significantly more Q-Pan H5N1 subjects in 002.

Again similar to 001, slightly more Q-Pan H5N1 subjects reported unsolicited adverse events than placebo subjects through day 42 and through day 84. When we drill down and look at these unsolicited events, we see that the most common imbalances -- though there were other imbalances -- the most common occurred in the number of Q-Pan H5N1 subjects who reported injection site reactions, specifically pruritis and warmth, and also there was an imbalance in the number of subjects who reported insomnia. We'll see later why that may be important.

When we look at medically attended events, we see a similar proportion of subjects reporting medically attended events in each of the treatment arms through days 42, 182, and 364. SAEs were similar in terms of reporting rates.

However, when I drilled down and looked at SAEs by type through day 182, I noticed that there were a handful of SAEs that occurred exclusively in the Q-Pan group, and in greater than the 3-to-1 randomization ratio.

Those were myocardial infarction, in five subjects, intestinal obstruction, in four subjects, and pulmonary embolism, in three subjects.

By day 364, two MIs had occurred in the placebo group, negating the imbalance between the Q-Pan arm and the placebo arm. However, Q-Pan-only intestinal obstruction and PEs remained. We added thyroid cancer and convulsions to that list.

I have listed these events out here for you. I'm not planning to go through this table in any sort of detail. I will simply say that three of the four subjects with intestinal obstruction clearly had comorbid conditions that could have easily predisposed them to this outcome. The cases of pulmonary embolism, convulsion, and thyroid cancer do not have the same type of comorbid predisposing conditions, but the 3-to-1 trial randomization may make this 3-to-0 event rate a chance happening. But I still wanted to point this imbalance out just for completeness' sake.

Moving on to nonfatal SAEs, all SAEs were deemed unrelated to vaccine by the investigator. However, there were four SAEs that, in the opinion of this reviewer, had a strong temporal relationship to vaccination and/or lacked an alternate plausible cause.

The first of these was in a 65-year-old female

with a history of hypertension not stated to be uncontrolled or requiring medication. She had two SAEs, actually, on day 1 and day 9. She experienced cerebrovascular accidents on day 1 and day 9 post the second dose of active vaccine. She had ischemic infarcts that were confirmed via CT. These conditions were reported to have resolved, with sequelae, four and ten days, respectively, after onset.

The second case is that of a 59-year-old male without recorded past medical history, who experienced a pulmonary embolism on day 21 post-dose 1. He is actually accounted for in the table that I presented in the slide before.

The next case is that of a 52-year-old female, status post-corneal transplant 18 years prior, who had a left corneal transplant rejection on day 103 post-dose 2.

The last case is that of a 63-year-old male with right-sided abdominal pain requiring exploratory surgery on day 143 post-dose 2, who had pathology consistent with inflammatory changes and thickening of the cecum.

With regard to death, there was one death through day 42, and that occurred in a 59-year-old male with a past medical history of diabetes and hypercholesterolemia, who had a fatal MI 17 days post-dose 1 of Q-Pan H5N1. No autopsy was performed. This death was deemed unrelated to

vaccine by the investigator.

Through day 364, there was a total of 11 deaths. Four occurred on the Q-Pan H5N1 arm and seven on the saline placebo arm. I have listed the causes there for you.

To summarize the safety of Q-Pan H5N1 from studies 001 and 002: We saw more frequent local and systemic reactogenicity, and we even saw more severe reactogenicity locally in both 001 and 002 and systemically in 001. Lastly, there were imbalances in reported adverse events in both expected events -- namely, injection site reactions -- and also in unexpected events.

We need to keep in mind that these unexpected events may be due to the 3-to-1 randomization and the fact that the frequency of all of these events is small. Keeping all of that in mind, the clinical relevance of this imbalance is uncertain.

Moving on to additional safety evaluations, GSK performed some additional evaluations per CBER’s request and as part of its routine surveillance of adverse events associated with its novel adjuvants.

The first of these was a screening of safety databases for selected neuroinflammatory, musculoskeletal, gastrointestinal, metabolic, skin, and autoimmune disorders. We refer to these as adverse events of special interest or potential immune-mediated diseases. The

adverse events of special interest were originally defined back in 2009 in the European Medicines Agency's Committee for Medicinal Products for Human Use risk-management plan for pandemic vaccines for safety monitoring. Subsequently, GSK included additional preferred terms and standardized MedDRA queries in a list of potentially immune-mediated diseases. Overlap exists between the two lists.

This slide includes the specific search terms. I'm not going to go through it. It's simply here for your reference.

In 002, a total of 15 subjects, 14 Q-Pan H5N1 subjects and 1 placebo subject, reported 16 AEs of special interest, or pIMDs. GSK and CBER agreed that the following Q-Pan H5N1 cases had alternate plausible causes. Those are one each of polymyalgia rheumatica, lumbar radiculitis, rheumatoid arthritis, Crohn's disease, celiac disease, and rheumatoid lung.

I will present the remainder of cases in the next few slides, as these are cases in which GSK and CBER either disagreed that an alternate plausible cause exists or we agreed that no other plausible cause exists. The first three cases I will present are cases where GSK and CBER disagree on the presence of an alternate plausible cause. I need to stress at this point that the lack of an alternate plausible cause is not synonymous with a

determination of vaccine relatedness or causation.

The first case was a report of a cranial nerve IV palsy in a 77-year-old male with a history of hypertension. The cranial nerve IV palsy occurred 22 days after the second dose of Q-Pan H5N1. GSK considered that hypertension was a likely cause. Although isolated cranial nerve palsies do occur in association with hypertension, there is no evidence that this subject had uncontrolled hypertension at the time of diagnosis, nor did he have any stigmata of poorly controlled hypertension. So I believe that the temporal association with vaccination makes a hyperinflammatory response to vaccination leading to a microvascular event a more plausible explanation. So we disagreed in this case.

The next case is a case of PMR that occurred in an 84-year-old woman. Dr. Arellano actually referred to this case in his presentation. This subject had new-onset back pain two days post-dose 1 and new-onset neck and shoulder pain 82 days post-dose 2, with a documented increase in sed rate. For some reason that’s not explained, the principal investigator, after the database lock point, decided to -- she was given initially a diagnosis of PMR, but the principal investigator decided to change that diagnosis to fibromyalgia after the database lock point. So we disagreed here.

The last case in which we disagree about the presence of an alternate plausible cause, and probably the most controversial of the cases, is that of a 28-year-old male who was diagnosed with autoimmune hepatitis. This gentleman, according to his medical records, was urged by his wife, probably about 40 days after his second dose, to go to his medical doctor to have lab work done. He presented to his physician and he had some lab work done, which included chemistries. Actually, in the original presentation of his story, it said that his wife urged him to go have chemistries done. Those chemistries showed that he had mild to moderate elevation in his liver enzymes. It also showed that he had a total bilirubin of 2.6.

You may imagine that his wife may have urged him to go seek medical care because he was, in fact, icteric, with a bilirubin of 2.6.

His workup eventually included serologies that showed that he had anti-smooth muscle antibody at titers of 1 to 5,120. He subsequently went on to have a biopsy that was at least suggestive of autoimmune hepatitis.

There were no laboratories done at baseline in 002, but he did have baseline serum that was stored and was tested. This was tested after his diagnosis that was suggestive of autoimmune hepatitis. He was found at baseline to have an anti-smooth muscle antibody titer of 1

to 320 and normal LFTs.

I don't dispute that there was something present at baseline in this man. There’s a question, though, of whether or not his baseline disease was exacerbated potentially by his vaccination. There are no other plausible causes for his increase in titers and his increase in liver enzyme and his hyperbilirubinemia.

For the remainder of the cases neither GSK nor CBER identified an alternate plausible cause. There’s a case of psoriasis, a case of erythema nodosum, a case of temporal arteritis, facial palsy, lupus, and vasculitis, all in the Q-Pan H5N1 arm. Then there was one case of psoriasis in the placebo arm.

Moving on to the integrated summaries of safety, GSK performed two integrated summaries of safety. You all heard these integrated summaries of safety presented earlier today. The first one was ISS-1. It was conducted in 2009. It included safety data from eight Q-Pan and D-Pan H5N1 controlled and uncontrolled studies, including approximately 12,000 adult subjects, 9,873 of whom received H5N1 plus AS03 and 2,408 who received either active control of unadjuvanted H5N1, or Fluarix, or saline placebo control.

The ISS-2, which was conducted in 2011 to expand the safety data -- I apologize for this typo. It’s correct

in Dr. Arellano's slides. It's 28 studies, not 24 studies. It included Q-Pan and D-Pan H5N1 and H1N1 controlled and uncontrolled studies, including 22,521 adult subjects, 16,000 of whom received H5N1 or H1N1 plus AS03 vaccine and approximately 6,000 who received an active control, either unadjuvanted H5N1, Fluarix or FluLaval, or saline placebo.

Going right to the ISS-1 results, solicited adverse events were reported similarly to events in the pivotal clinical trials in terms of frequency and severity. It was noted that mild temperature elevations occurred twice as frequently in H5N1 plus AS03 subjects versus control subjects. H5N1 plus AS03 subjects reported more solicited injection site reaction -- injection site warmth, injection site pruritis -- malaise, nausea, insomnia, and dizziness. All reported potentially immune-mediated diseases were in the H5N1 plus AS03 arm, and they totaled 17 cases.

Five of these cases were already captured in 002 and I have presented them to you. There are two cases of PMR, the case of cranial nerve IV palsy, one case of psoriasis, and a case of erythema nodosum.

There were 12 additional cases, not previously captured in 002 or reported in my presentation. I will discuss these in the next few slides.

In the ISS-1, there were two cases where GSK and

CBER disagreed as to the presence of an alternate plausible cause, one case each of facial paresis and neuritis, where GSK did not identify an alternate plausible cause, but dismissed the idea of an immune-mediated response due to the fact that these events occurred on the day of immunization.

For the remainder of the cases, neither GSK nor CBER identified an alternate plausible cause. Those included two cases of PMR, a case of Grave's disease, a case of uveitis, a case of scleroderma, a case of facial palsy, Bell's palsy, facial weakness, psoriasis, and multiple sclerosis.

Moving on to the ISS-2, there were a number of additional reports of diagnoses previously discussed. I have listed them here on the left-hand side. Some of these had alternate plausible causes. Others did not. But because we have at least seen these diagnoses in 002 or the ISS-1, I did not want to spend any more time reviewing similar cases. Instead, I thought I would spend a little time on diagnoses not previously discussed.

There were additional cases for autoimmune thyroiditis, three thrombocytopenias, two ulcerative colitis, and then one each of a couple of cranial nerve palsies, optic neuritis, ankylosing spondylitis, Raynaud's phenomenon, and Stevens-Johnson syndrome. Many of these

cases had alternate plausible causes. In the next slide I will present the cases for which neither GSK nor CBER identified an alternate plausible cause.

Those are the cases of MS, a case of ITP, a case of ulcerative colitis, a case of ankylosing spondylitis, a case of Raynaud's phenomenon, autoimmune thyroiditis, and Basedow's disease. You will note that several of these events occurred quite some time from the vaccination, but were still captured. That's because these subjects were enrolled in booster studies or alternate-schedule studies, so they were still being followed.

Moving now to the postmarketing safety experience with related products, GSK marketed two AS03 adjuvanted pandemic vaccines outside of the US during the 2009-2010 pandemic. Pandemrix H1N1 was manufactured using the Fluarix manufacturing process. Approximately 173 million doses were distributed during the pandemic and an estimated 31 million people received Pandemrix.

Arepanrix H1N1 was manufactured using the FluLaval manufacturing process. Approximately 171 million doses were distributed, and an estimated 59 million people received Arepanrix.

GSK conducted specific analyses to assess postmarketing safety of Pandemrix and Arepanrix for a number of safety concerns. I have listed them here for

you. Of all of these, three analyses resulted in findings that warranted labeling changes. The analyses of pediatric safety data revealed that febrile convulsions were the most common serious adverse events reported after Arepanrix vaccination in children. That was the most common SAE in both 0-to-2-year-olds and 3-to-9-year-olds, with an event rate of 1 per 1 million vaccinated and 0.5 per 1 million vaccinated, respectively. These results resulted in febrile convulsion being added to the Arepanrix H1N1 reference safety information.

The analysis of Guillain-Barre syndrome reports showed that there was a higher observed-to-expected number of cases following Arepanrix vaccination, and so GBS was relocated in the Arepanrix RSI to be listed as reported with Arepanrix H1N1.

Lastly, I will briefly discuss narcolepsy and Pandemrix. You heard a lot about narcolepsy from Dr. Arellano already.

There were increased postmarketing reports of narcolepsy post-Pandemrix H1N1 vaccination. Studies in Finland, Sweden, and Ireland identified a 6- to 13-fold increased risk of narcolepsy in children and adolescent post-vaccination, which resulted in 3 to 7 excess cases per 100,000 vaccinated.

As a result of these findings, GSK added

narcolepsy to the warnings and undesirable effects of the Pandemrix EU summary of product characteristics, which is their label. This led to restricted use in persons less than 20 years old.

Just some general information about narcolepsy. Again you have heard some of this already from Dr. Arellano. Narcoplepsy is a disorder of sleep-wake control in which elements of sleep intrude into wakefulness and elements of wakefulness intrude into sleep. Sleep maintenance insomnia is very common in narcoleptics, and narcoleptics can actually be misdiagnosed initially as insomniacs. I bring that up because we have seen throughout the safety database these slight imbalances where insomnia continues to pop up.

Narcolepsy manifests as daytime sleepiness with or without cataplexy, hypnagogic hallucinations or sleep paralysis. Narcolepsy with cataplexy has an estimated prevalence in the US of 25 to 50 per 100,000 persons and an estimated incidence in the US of 0.74 per 100,000 person-years.

Narcolepsy with cataplexy is typically diagnosed in teens and persons in their early 20s.

Narcolepsy may be triggered by immune activation and has a strong HLA association.

Moving quickly to GSK’s pharmacovigilance plan --

again, you have heard a much more recent update from Dr. Arellano, so I will just run through this very quickly.

GSK submitted a pharmacovigilance plan to the BLA. It includes both passive surveillance and an active surveillance plan. The passive surveillance plan is to be conducted during the pre-pandemic and pandemic periods. It includes:

• Routine data collection on all adverse event reports.

• Global literature review, periodic distribution, and safety reports.

• Disproportionality analyses for signal detection, which in the pre-pandemic period they will do monthly and during the pandemic, would be done weekly.

• Close monitoring of Bell's palsy, convulsion, demyelinating disorders, encephalitis, GBS, neuritis, vasculitis, vaccination failure, narcolepsy, autoimmune hepatitis, and increased concentrations of transaminases.

Their active surveillance again would be performed during the pandemic period and includes the pandemic cohort safety study that you heard Dr. Arellano discuss -- and that data, wherever it's conducted, will be shared with the US -- a pregnancy registry, and GSK has also committed to working with the US government to evaluate safety.

In summary with regard to immunogenicity, the proportion of subjects achieving seroconversion and HI titers greater than or equal to 1 to 40 after two doses of Q-Pan H5N1 21 days apart exceeds CBER's suggested immunogenicity criteria for accelerated approval of a pandemic vaccine.

With regard to safety, there is significant local and systemic reactogenicity associated with Q-Pan H5N1. Pain was far and away the most frequent solicited event. However, all solicited events appeared to be transient and none of them required medical attention.

Lastly, there appears to be an imbalance in reporting frequency for unsolicited AEs, SAEs, and AEs of special interest and potentially immune-mediated diseases. The significance of these imbalances is unclear, due to the rarity of events both within the pivotal studies and in the general population, and the size of the study populations.

With that, I would like to say thank you. It takes a village to raise a VRBPAC presenter. I would like to say thank you to the Q-Pan review team, the DVRPA and OVRR management, and the OBE reviewers who helped me tremendously with this presentation.

With that, I will present the questions to you again quickly so that you can think about them during lunch.

The questions that we have for the committee today:

1. Do the immunogenicity data support licensure of the Q-Pan H5N1 vaccine for use in adults at increased risk of exposure or during a pandemic? Please vote yes or no.

2. Do the safety data support licensure of the Q-Pan H5N1 vaccine for use in adults at increased risk of exposure or during a pandemic? Please vote yes or no.

The last one is really a discussion topic, which you will not be asked to vote on. Please discuss the following two approaches to confirm the effectiveness of Q-Pan H5N1 for traditional approval. One is to confirm the clinical benefit of Q-Pan H5N1 with efficacy data generated with a US-licensed seasonal influenza virus vaccine made according to the same manufacturing process, or two, to confirm the clinical benefit of Q-Pan H5N1 by conducting an effectiveness study or studies during an H5N1 influenza virus pandemic.

With that, I will end.

DR. DAUM: Thank you very much, Dr. James, for going through a very large amount of data in a very short time.

We have a couple of minutes for clarifying questions for Dr. James. Dr. Levandowski.

DR. LEVANDOWSKI: It’s actually a question for either Dr. James or for GSK. Is there information on resolution of narcolepsy in those individuals who were being studied before, in the Swedish and the Finnish studies?

DR. DAUM: Do you want to tackle that first, Dr. James?

DR. JAMES: I’m going to let GSK tackle that.

DR. DAUM: Does GSK want to tackle that?

DR. SHINDE: Vivek Shinde, influenza epidemiologist at GSK.

What is being done is that the investigators are conducting long-term follow-up studies to understand if there are differences between vaccinated and unvaccinated cases and what impact that could have on prognosis.

DR. LEVANDOWSKI: I was actually wondering more about the clinical course and whether one expects that narcolepsy will resolve at some point.

DR. SHINDE: Sorry, I didn’t understand the question.

DR. SEIFERT: I’m Harry Seifert, from clinical safety and pharmacovigilance.

Our current understanding of unvaccinated narcolepsy is that it’s essentially a chronic condition, and although it can change over time, it usually doesn’t

heal or go away.

DR. DAUM: I’m sorry, but that’s still not the answer to the question, as I understood it. The question, as I understand it, for FDA or for the manufacturer is, in those cases that were identified after vaccinated, what are the people doing now? Are they sleeping or are they awake? Is this going on?

DR. SEIFERT: Our understanding is that those patients continue to have narcolepsy.

DR. DAUM: Thank you very much.

DR. LEVANDOWSKI: A second question related to Guillain-Barre syndrome. Dr. James mentioned that reference material for Arepanrix was changed. The comment was that the observed number of cases was increased over the expected number of cases. But is that the expected number of cases for an influenza vaccine or the expected number of cases for the population under study?

DR. DAUM: To whom is that question directed?

DR. LEVANDOWSKI: It could be either Dr. James or GSK, because they may know more about it than Dr. James.

DR. JAMES: If it’s okay, I would like to defer to GSK for that one.

DR. DAUM: Anything is okay.

DR. JAMES: Okay. Then I would like to defer to GSK. This is their information that I’m presenting to you.

DR. ARELLANO: I think Dr. James was referring to one particular paper of GBS. I think it would be good to have information on GBS in its totality.

I want to show two slides. This is actually a summary slide that shows the epidemiological studies that have been performed, in this case with non-adjuvanted vaccines. As you can see in the right-hand column, most of the point estimates are increased and most of them don't include 1s. It means there is statistical significance -- not all of them.

The next slide, S35. This is the same data for adjuvanted vaccines. In this particular case most of the point estimates are around 1, and they do include 1.

The paper that Dr. James was referring to is the DeWals, in Canada. But I would also like to point your attention to the paper by Weibel, which is a global meta-analysis. Here the authors show a pooled adjusted relative risk for the adjuvanted vaccines which was lower and not statistically significant compared to the non-adjuvanted vaccines.

So I think the information on GBS has to be taken as a whole.

DR. DAUM: Does that answer your question?

DR. LEVANDOWSKI: Yes.

DR. DAUM: Other clarifying questions based on

the data that you have heard from Dr. James. Dr. Marcuse.

DR. MARCUSE: Dr. James, on slide 76, you have the intriguing note that narcolepsy may be triggered by immune activation and has a strong HLA association. Could you just say a sentence or two about that?

DR. JAMES: I think Dr. Arellano said earlier that there’s a lot that we don't know about the pathogenesis of narcolepsy. Again I think it has been postulated, but not confirmed that narcolepsy can be an autoimmune event. That would be the association with immune activation triggering. Then the strong HLA association -- my understanding is that -- I want to say this correctly -- that subjects with narcolepsy quite often have this HLA-DQB1 0602 HLA type. But the reverse is not true.

DR. DAUM: Saying “I don't know” is just fine. But do you have knowledge of the immune activation events that are being referred to in that paper?

DR. JAMES: No. No specific events that I read were cited.

DR. DAUM: Does GSK want to comment on that?

DR. ARELLANO: I didn’t get the question.

DR. DAUM: On the slide that we’re looking at, the last bullet says that narcolepsy may be triggered by immune activation, and there’s a reference there. The

question is, in that reference, what immune activation is being discussed?

DR. ARELLANO: I'm not aware of the -- what we know is that basically the presence of the HLA is a necessary condition, but is not a sufficient condition. There have been postulations on influenza infection, H1N1 infection. But how that triggers immune activation I'm not aware.

DR. DAUM: Let's perhaps move on. Dr. Gellin.

DR. GELLIN: You have introduced a huge topic before lunch -- this whole issue of triggering an immune activation for a whole bunch of stuff. I think they are credited to look hard for a series of diseases that fall broadly under autoimmune because there's this concern about it. But I wonder whether or not we're going to have an opportunity to actually understand what is known and not known about triggers of these kinds of diseases.

In Dr. Golding's presentation, under risks and benefits, the slide says risks include nonspecific immune activation. But her narrative said these were potential and things that were going to be looked for.

Again, I think this is all -- I guess I would like to understand the degree to which this is theory and plausibility versus actual. I think this is a huge issue for this field generally, and the degree to which we can

have some information about how to tackle this -- I think we are going to have recurrent discussions about adjuvants and these kinds of events.

DR. DAUM: I think you raise a good point. I'm asking a clarifying question, and that is, what is in that reference that supports that statement. We're not going to get the information right now, but we'll try to get it later.

Okay, I see no more hands up. That means it's lunchtime. We're going to turn the floor over to Mr. Jehn for an announcement or two.

But I would caution the committee that these questions which will be discussed and voted on this afternoon should not be discussed at lunchtime among committee members.

With that, I'll turn the floor over to Mr. Jehn.

(Administrative announcements)

DR. DAUM: It's 12:50 here in the Eastern Time Zone. We will have a one-hour lunch and reconvene promptly at 1:50. Thank you.

(Recess for lunch)

AFTERNOON SESSION

DR. DAUM: Before we move into the open public hearing, the sponsor has requested a second opportunity to respond to two questions that came up this morning. They promised they would be brief. This is their time. You're on.

Be sure that whoever is speaking tells us which questions they are responding to.

DR. WETTENDORFF: Martine Wettendorff, vaccine development leader at GSK.

I couldn't hear very well the question regarding the immune activation behind the narcolepsy disease and what might be potentially the immune mechanism. In short, what is described in the sleep paper that was referenced in the FDA presentation is indeed the fact that the key element that has led investigators to suspect an immune mechanism in narcolepsy is a very strong association with the HLA DQB1 0602 with narcoleptic patients. There have been several hypotheses put forward, some being that narcolepsy is an autoimmune disease or an immune disease directed to external antigens, antigens from infections that have been described in the literature. Strep infection can be associated with narcolepsy, and also influenza infection.

There have been several investigations leading to

conflicting data regarding autoimmune diseases. No specific classical markers for autoimmune diseases could be found in narcoleptic patients, some autoantibodies to specific neuronal cells have been found, but it’s not clear if they are really associated with the disease as a marker or really the cause, as it is likely that if there is an immune cause, it is more likely to be T cell-related due to the strong HLA association.

These are hypotheses at this stage. The exact etiology of the disease is unknown and is very likely to be multifactorial. However, this immune mechanism hypothesis has been taken into account in our research plans.

If I can remind you quickly, we have two major axes in our research plan. The first axis is additional epidemiology studies, with the key objective to confirm this narcolepsy signal observed as narcolepsy. It has not been confirmed yet. The second axis is more basic research with a working hypothesis that narcolepsy might be an immune disease leading to destruction of hypocretin-secreting neurons.

I hope this clarifies the question regarding the immune mechanism. If we have time, we would like to clarify also -- I think there was a question regarding the potential biological plausibility of an adjuvanted vaccine in the context of narcolepsy. I would like to call my

colleague Nathalie Garcon to address this point.

DR. GARCON: Nathalie Garcon, Adjuvant Center.

I didn’t hear at all the question, so I apologize. I just want to complete on what Hana Golding presented this morning on the mode of action of AS03. In order to have an -- disease, several factors are needed to appear at the same time. You need a predisposition, genetic predisposition. You need to have the self-antigen being either excreted if it’s internal or presented. You need activation of antigen-presenting cells at the level of the target organ. You need activation of T or B cells.

If we look at all those different steps in an autoimmune disease, we know through the preclinical toxicology evaluation that there is no microscopic -- we don't have any signal that indicates inflammation at the level of the brain, of the meninges. Through biodistribution by a radioactive component of the emulsion, we cannot find either the AS03 adjuvant or any of its constituents at the level of the brain. Those data tell us there’s no chronic inflammation that we can find at the level of the brain and also that the adjuvant cannot induce an innate immune response at the level of the brain.

Through the mode of action of AS03, we have looked at the possibility of the adjuvant to directly activate T and B cells. We have done that through

different *in vitro* experiments in human cells, purifying out from PBMCs, CD40 cells, CD80 cells, and B cells. Through those experiments, we could not identify at any doses we tested, which were from one-half to one-fifth of the human dose -- we could not see any activation of those cells, either at the resting stage or at the preactivation state.

All those data put together with what Hana explained this morning do not indicate to us that there is a biological plausibility that AS03 could cause narcolepsy.

DR. DAUM: Thank you very much.

We'll now move to the open public hearing portion of the meeting, for which there is currently no one scheduled to speak. Nevertheless, in support of the rules of the activity that we're doing here, we will make available this time. A few statements regarding it. Mr. Jehn.

Agenda Item: Open Public Hearing

MR. JEHN: 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.

Does anyone from the public wish to speak?

(No response)

It appears not, Dr. Daum.

DR. DAUM: So that saves everyone from listening to me read a whole page of statement about the open public hearing.

We'll now move on to the afternoon's deliberations, lacking speakers at the hearing.

Agenda Item: Committee Discussion and Vote

What we're going to do is consider questions. I wonder if somebody could put the questions up on the screen for us to look at while we talk.

What I would like to do is to have committee members speak to whatever issues they like with respect to the morning's presentation. After we get a semblance of how people are thinking and feeling, we will move on to the questions per se. The first two questions require votes, and then there are several discussion items as well. Perhaps you recall those, but hopefully we'll see them soon.

So I would like to ask committee members to begin the discussion. They can literally raise anything on their minds that's germane to the morning's presentations and the afternoon's consideration. Who would like to start?

DR. GRAY: This question is for Dr. Innis. You suggested that there was some neutralization data that you guys had prepared. I was just wondering if you could maybe

summarize that, how that looked with the HI RBCs.

Also you suggested that there might be some cross-protective response with the product. Just a summary would be nice.

DR. INNIS: I'm often longwinded. I'll try to be very concise. But I do have five slides I want to show you. Could we start with E2?

This is a ferret study, in which ferrets immunized with A/Indonesia were challenged with A/Vietnam wild-type virus -- I'm sorry, the other way around. Immunized with A/Vietnam vaccine, challenged with wild-type Indonesia, 100,000 ferret lethal doses intratracheally. What you're looking at here are vertical bar charts of lethality. Animals were immunized twice, allowed to rest for a short period of time, and then challenged. So this is an acute challenge study.

In the controls, which were unadjuvanted vaccine and AS03 alone, there was 100 percent lethality. In a half-human dose, 1.9 -- it's labeled 1.7 micrograms of hemagglutinin with AS03 -- one of the six ferrets in that group died, but all the animals who received the human dose that's under consideration today, as well as higher doses with AS03, survived. That's the survival. The plot is looking at virus recovered from their lungs. There was a marked decrement between the animals who died and those

animals that were examined and were alive at the time of euthanasia, about a 4-log decrement in virus.

This is the evidence that there is cross-protection. We can't assess cross-protection in humans, but we can show you cross-reactive neutralizing antibodies.

The next slide I would like to look at is E7.

Just to orient you to this slide, these are people who participated in the first clinical trial, 001. Subgroups were studied for neutralizing antibody. The top row is A/Indonesia. It's the homologous responses, and we're looking at geometric mean titer of 1,500, seropositivity 92 percent, and the threshold for this assay is 1 to 28. Then we're looking at what we call the vaccine response rate, the proportion of individuals who made at least a fourfold response. For instance, if someone was seronegative, then they were assumed to have a titer of 1 to 14, and they should have met or exceeded a 1-to-56 titer. That was 97 percent.

So those are the homologous responses.

Indonesia is clade 2.1 and is absolutely antigenically unrelated to A/Vietnam, which is clade 1. So you see that there the titers geometrically are 260, with 92 percent seropositivity following two doses and 53 percent making that fourfold response.

When you look at Anhui and Turkey viruses as the

viruses which the post-vaccination sera are asked to neutralize, these are in the same clade as Indonesia, but in a different subclade, and the responses are proportionally better.

The next slide I would like to show you is E18.

The reason there’s cross-protection and the reason that there’s long duration and the reason that we can heterologously boost people is because we induce CD4 T cells that are specific for the vaccine antigens. We’re looking at the absolute increase in cells per million that are vaccine-specific. We have taken the baseline value and subtracted that from the day 42 value for four groups of patients that were in the D-Pan antigen dose-finding study. We’re looking at people who received 3.8 or 7.5 micrograms of unadjuvanted antigen, as the first two bars, and then those same two antigen doses with the adjuvant in the second two bars. Focus on all doubles, which means that the CD4 T cells needed to express any two of those four cytokines that are listed there -- CD40 ligand, interferon gamma, IL-2, or TNF-alpha. The all-doubles proportion is thought to be a surrogate for what kind of central memory is being created. You see that there’s a profound difference between the unadjuvanted and adjuvanted arm.

Now I would like to show you slide E13, which looks at the persistence of antibody. This is HI antibody.

These are age strata in the pivotal immunogenicity study, young adults, elderly adults, and the elderly subset that's older than 75, going from left to right. You are looking at geometric mean titers and seroconversion rates. The two figures that are labeled are the proportion at day 42 and then the proportion at six months. So there is reasonably good preservation of circulating antibodies in terms of immune response.

But more importantly, I want to show you the evidence which says there's good memory that can be induced with a heterologous challenge. Let's go to slide E15.

This is a complicated slide, but there's a very simple message to it. In this study individuals received a single dose of the candidate vaccine, and either six or 18 months later, were given a dose of A/Turkey with adjuvant. There's a single priming dose with adjuvanted vaccine. You are looking at geometric mean titers of antibody to A/Turkey. There is relatively limited cross-reactive antibody to A/Turkey after receiving a single dose of A/Indonesia. But within ten days of receiving a boost, you see profound responses for all groups, whether they were boosted at six months or 18 months later. This is the evidence that there is boostable memory over the long term.

Lastly, I want to show you, from the main presentation, slide A-33. This is the Kaplan-Meier

disease-free survival proportion. Look at the blue line. These are cases of H1N1 disease occurring in recipients of two doses of Q-Pan versus controls, in the green. You see that cases occurred throughout the one year of follow-up, in the green set, the control set, but not in the blue set. This is evidence that says clinical protection, freedom from disease, persists over a long period of time.

I hope that answers your question.

DR. DAUM: Thank you very much.

More committee questions? Go ahead, Dr. Piedra.

DR. PIEDRA: I have two questions for GSK --

DR. DAUM: Let me clarify one thing before you start. People on this side of the table -- I have had a request from the sponsor -- they claim they cannot hear. What I would like you to do is rudely turn your back on them and speak directly into the microphone. That way everybody will hear the question and I think there will be no ambiguity.

DR. PIEDRA: Again, I have two questions for GSK. The first one is if they could clarify what the differences are in the way that the FluLaval from Fluarix is prepared, Quebec versus Dresden.

The second question has to do with the quadrivalent FluLaval, if they have data to elucidate whether there are differences in the efficacy of the

vaccine over time. Is the vaccine efficacy the same early into the flu season compared to later into the flu season? That really has to do with the issue of antibody decrease over time.

MS. BOYCE: We'll respond to your first question. Dr. Martine Wettendorff will address the differences between the D and the Q manufacturing process. Then I'll have Dr. Innis come to the microphone to address your questions with regard to differences in the efficacy.

DR. WETTENDORFF: Your question was, what are the manufacturing differences between our FluLaval and our Fluarix processes? Maybe I can have the slide up, please.

There are actually minor differences in the manufacturing processes between the two vaccines. Both processes yield to an inactivated split-virion antigen. There are no differences at the level of the upstream process. There are differences at the downstream process level and at the level of formulation. Mainly, as you can see on this slide, the differences are related to the sequence and the methods of inactivation for the two vaccines. For the Quebec vaccines, we have first an inactivation by UV, followed by formaldehyde, and the purification is done by centrifugation and disruption with deoxycholate, leading to the split virus, while in the Dresden process, the virus is concentrated and purified by

zonal centrifugation, and it’s further purified by filtration and then inactivated with the consecutive effects of deoxycholate and formaldehyde.

At the level of the formulation, there are excipients that are added in the Dresden manufacturing process. We have polysorbate 80, Triton X-100, and magnesium chloride that are added as excipients in the Dresden formulation.

This is the information you can find, the USPI for both FluLaval and Fluarix vaccines.

DR. DAUM: There’s a second question.

DR. INNIS: Could I have slide E30?

You asked about decrement in antibody responses and whether that is potentially related to any loss of protection over six months of follow-up in the quadrivalent vaccine efficacy trial.

First I want to show you the acute antibody responses to assure that there was active immunization that was approximately equal for all four strains included in the vaccine. A random subset of children also had blood collected at 180 days. These samples were also tested. I don't have a plot of the data, but the geometric mean titers at the end of the observation period declined by approximately 50 percent.

There is a cumulative hazard plot. I don't have

that with me either, so you have to trust me on this. There were cases in the control group throughout the six months of observation, and there was no evidence, looking at the plot, of convergence of the vaccine group versus the control group.

I should say that most of the countries that participated in this trial have a period of transmission of several months during the rainy season. These are all subtropical or tropical countries. So the peaks of transmission were typically June through August. Children were immunized in March.

We're very confident that this vaccine offers at least six months of sustained protection. This is the unadjuvanted vaccine.

DR. DAUM: Thank you very much.

Other committee questions? If there aren't any, we'll go to the questions. Dr. McInnes.

DR. MCINNES: I have a question, just trying to understand a little bit more about traditional approval and accelerated approval. I think Melinda asked the question this morning about strain change and whether there was a difference in how a strain change would be viewed between a traditional-approved product and an accelerated-approved product. I believe that answer was no difference. Is that correct?

DR. GRUBER: Yes, that would be correct. A vaccine that is approved using the accelerated approval provisions -- you have safety and immunogenicity data. The confirmatory study is usually ongoing. If we then enter the phase where we do a strain change and approval thereof, the strain-change approval uses the same process, and no additional data that are needed for vaccine that is approved via accelerated approval provisions versus traditional approval.

DR. MCINNES: The second question is around intent of use of this pandemic monovalent. Is it correct that this will be delivered to the government and will be held in the stockpile until such time as there is a signal that it would be used? There is not at this point a plan to pre-immunize the population?

DR. GRUBER: I think this is a question that can not only be answered by the FDA. You perhaps need to call on Dr. Robinson to further elaborate here. However, what I want to stress and make clear is that the pathways to licensure that the FDA discussed in February of 2012 with this committee and that we briefly reviewed this morning really pertain to products that are used during a pandemic. We didn’t entertain pre-pandemic use or using this product before there is a declaration. That is what we stated in February and this is what I would like to stress here.

DR. MCINNES: So that’s still consistent. We’re looking at pandemic use.

I was looking at some of the diagrams of the paths, and I think it’s very clear to me that for the seasonal -- first of all, I think it’s consistent with our discussions. I felt very strongly back in February that having the same manufacturer who makes a seasonal vaccine for licensure in this country be someone who makes the pandemic vaccine, because we have this comfort level with the process, the rigor that it goes through. We have what I think I called the gestalt. We understand the performance over many years of looking at these kinds of vaccines.

I understand from the seasonal vaccine that the path could kind of be two ways. You would have your safety and immunogenicity data, and at some point efficacy is demonstrated, and you could have a full traditional approval.

What I don't really understand is why it’s necessary for the pandemic candidate to drive all the way to traditional approval and why it could not halt at accelerated approval, with a rigorous body of safety data and immunogenicity data, but absent demonstration of clinical endpoint efficacy or inference of clinical endpoint efficacy from the seasonal vaccine. What are the

nuances of not having them parallel all the way down, one at one stage and one at another stage?

DR. DAUM: I think FDA should answer that question first, if you don't mind -- not that it’s simple.

DR. GRUBER: Not that it is simple, that is true.

First of all, Pamela, yes, you could license a pandemic influenza vaccine using the accelerated approval provisions. You say what I need at the time of approval is safety and immunogenicity data. The point is that the accelerated approval provision -- there is a requirement to confirm the clinical benefit of the vaccine. So that’s our regulation. You could argue that you can interpret the regulations by saying, okay, let’s confirm the clinical benefit at a future time point -- let’s say during a pandemic -- or you can say, what other scientifically supportable pathway can be chosen, especially those where we have regulatory precedents?

FDA thinks if we approve a vaccine under accelerated approval regulations, we have to provide the applicant with a path forward that is feasible and doable. By saying that we give you an accelerated approval and we’ll see what happens during a future pandemic, perhaps you can or cannot do a clinical endpoint efficacy study or you cannot confirm the benefit, instead of not giving them a very clear path forward. But by saying -- and we had the

discussion in February -- that we will infer effectiveness of the pandemic influenza vaccine candidate by using the clinical endpoint efficacy data gained the seasonal vaccine that is manufactured using the same process, we, based on the scientific data available, feel that is a scientifically supportable path, and it is consistent with regulatory action, Pamela, that we have taken before, and that is the H5N1 Sanofi Pasteur pandemic influenza vaccine that we have licensed. We did not invoke the accelerated approval regulations there. We used traditional approval.

That does not exclude, as GSK has stated this morning, the commitment by the company of collaborating with parts of the government on plans to further evaluate the safety and effectiveness of the product during a pandemic.

That was a longwinded answer. My point is, if we approve a product under the accelerated approval regulations, there is a requirement to confirm the clinical benefit, and the path that we choose and the requirement that we put forth to the applicant has to be a study or studies that are feasible. That is, of course, what we can discuss further on in the afternoon: Is it feasible in the context of what we have heard this morning CDC presenting?

DR. DAUM: Do you want to follow up on that? It’s an important issue and I think we should air it.

DR. MCINNES: Thank you. This isn't easy for anybody. What causes me to pause is that H5 in particular has never been predictable for us. From 1997, it has always been unpredictable in terms of vaccine, in terms of response, in terms of doses that we needed. H7 and H9 may be equally predictable when we finally have to wrestle with them. I think what I'm struggling with -- and I appreciate the clarification, because I understand the philosophy and the logic -- what I'm struggling a little bit with is this inference that H5 is going to follow the rules.

DR. DAUM: Do you want to comment? I guess you do.

DR. GRUBER: Yes, I will comment. I invite others to chime in here.

Pamela, in so many ways, we had that very discussion in February when we were looking at the question: Can we extrapolate between subtypes? There was a lot of discussion. I actually have that right here in front of me. I think we all agreed that it is a complex issue. Do we have all the data that we would like to have? No, but we have data to suggest that it's reasonable to think that an extrapolation between subtypes is what we could do. That is because we have the HI antibody titer. We have seen data today that really suggests the immunogenicity of this vaccine. In so many ways, that's

what we have to bank on.

If you want to take it a step further, this is not any different from what we did in 2007 when we licensed H5N1. What you had for that product was safety and immunogenicity data, and it was an H5N1 vaccine. I have to say it really is in keeping, what we're suggesting today, with what we did there. We banked on the immunogenicity. We banked on this HI titer, which is thought to predict clinical benefit. That's what we did then. I think you were at that committee at that time. I'm sure you remember these discussions. That's what we're doing now.

DR. DAUM: There's someone else at FDA who would like to make a comment. Could you come to a microphone and tell us who you are?

DR. SUN: I'm Wellington Sun, director of the Division of Vaccines.

Since Marion asked for people to chime in, that's what I'm doing.

Dr. McInnes' question, I think, really strikes at the third question of today, which is the pathway to confirm effectiveness. I think it's truthful to say that we in FDA, the Office of Vaccines, have really struggled with this issue of licensing pandemic flu vaccines. It has evolved, I think. We are thinking that as the virus evolves, we perhaps need to evolve our positions as well.

The question of accelerated approval really hinges on the level of confidence in the HAI as a surrogate for preventing disease. Part of our struggle has been to find a way to infer effectiveness from one subtype to another, which would be what we are doing if we accept the FluLaval effectiveness study. The question is, can one infer effectiveness from one subtype to another? I think that is really the issue that we would like the committee to address.

DR. DAUM: Thank you very much. I agree with you completely that it is an issue we must address, but I think it's one of many, as opposed to "the" issue. I think the committee will have to deliberate and decide how it feels about it.

One of the things that I would like to do is to have people who haven't made comments make them. Certainly before we vote on the first question, I would like to hear from everybody about some issue. We're still in the sort of free-association phase of the afternoon discussion. This is your time. We'll ask people who haven't said anything to comment. Dr. Air, then Dr. Hudgens.

DR. AIR: There is a licensed H5 in one vaccine. We have not seen any comparisons in the data between that vaccine and the one that we're talking about at the moment. Can somebody give us some of those numbers?

DR. DAUM: That may or may not be appropriate. Does anyone from FDA want to comment on that request?

DR. WEIR: I'll just mention that in this morning's presentation, GSK made some reference to how their HI titers compare. Maybe they would like to repeat that.

You're right, there has never been a head-to-head comparison, but I think --

DR. INNIS: There was no head-to-head comparison. As Dr. Levandowski mentioned this morning, HI tests in the hands of one sponsor can differ. The most appropriate parameter to use in this kind of historical comparison would be to think about the seroconversion rate, because that's internally controlled. You're looking for a fourfold rise in titer from pre-vaccination to post-vaccination.

For the licensed H5N1 vaccine in healthy adults 18 to 64, the seroconversion rate was 43 percent. For GSK's vaccine in the same age group, the seroconversion rate was over 90 percent.

The geometric mean titer in the Sanofi product was 1 to 28. Here we really are limited by the lack of direct comparability of the assays, but the geometric mean titer in 001 in healthy adults was 400.

DR. DAUM: Thank you very much. Dr. Hudgens.

DR. HUDGENS: I have three comments or questions.

My first question is a clarification about the questions themselves and the phrase “in adults.” Is the question about this in adults at increased risk of exposure or in adults during a pandemic? In other words, during a pandemic would this be used in children as well or just in adults?

DR. DAUM: Do you want the questions dealt with one at a time or do you want to pose all three?

The question is about adults. I’m presuming from that that the agency wishes us to address the question as it is, but I think it’s fair game to raise the issue, what about children. If that’s your question, let’s see what people want to say about it.

DR. GRUBER: I really think that GSK should speak to this. The proposed indication is really in adults 18 years of age and older. That does not exclude, of course, that studies can also address the safety and immunogenicity of this in the pediatric population. But right now the data submitted to the BLA are really data that are generated in the adult population.

MS. BOYCE: We’re seeking an adult indication. We do have some data in children, if you would be interested in hearing about that.

DR. HUDGENS: That’s okay. I just wanted a

clarification on the question. I just wanted a clarification on the target population.

MS. BOYCE: It's for adults only.

DR. DAUM: How long will it take you to present the data in children?

MS. BOYCE: Well, it's Dr. Innis, so --

DR. INNIS: Not long. I'm prepared to be brief.

If the vaccine is licensed, we have an obligation under the Pediatric Research Equity Act to generate data in children. We have already begun that. Several thousand children have already been exposed to either Q-Pan or D-Pan.

Could I have the slide?

Look at the top. This is H1N1 studies performed in children, the middle row. There have been six studies completed so far, and 1,400 individuals have received the candidate vaccine at a pediatric dose. One of the studies was dose finding. Generally they have received half an adult dose.

The next study, HI antibody responses to the candidate vaccine with Q-Pan: This is the Phase III study that has been completed in children in the United States, Canada, and Thailand. These were children 6 months to 17 years of age. It's age-stratified. What you're looking at are geometric mean titers on a logarithmic scale. There

are three age strata, 6 months to less than 3 years of age, 3 years of age to less than 9, and then 9 to 17. You are looking at HI antibody responses pre-vaccination and post-dose 1 and then post-dose 2.

You see excellent antibody responses, higher than in adults, even though it’s a half dose, and highest of all in the very youngest children, where you would expect to have the least response.

The next thing I want to show you is injection site pain. It mimics the pattern seen in adults. There is pain. The reporting frequency is greater in older children, probably because they are better able to verbalize their experience. The blue bars are the vaccine candidate. Green is the saline placebo. So there are differences.

Lastly, fever, which is always critical in this kind of evaluation. This is age-stratified. We are looking really at children less than 6 years of age, where fever is a particular risk for febrile convulsions. There are two age strata for Q-Pan and then two age strata for saline. You are looking at dose 1 on the left-hand side of the graph and dose 2 on the right-hand side of the graph. The message here is that there are no notable differences in the frequency of fever when young children receive this vaccine -- no difference between treatment and saline.

I think that should be very reassuring for the pediatricians on the committee.

DR. DAUM: Thank you. It is reassuring. But perhaps Dr. Robinson might be a good person -- is he still here? I don't know the procedure. Is the government the correct group to require that studies be done in young children, before we leave this topic, or does the manufacturer just have to take the initiative?

DR. ROBINSON: We were established by Congress, and one of the things that we are required to do is have special population needs addressed, including children. In all of the projects that we have -- in this case, flu vaccines -- there have to be pediatric studies done. In many cases they have been done and are ongoing.

DR. DAUM: Thank you very much.

So today we’ll consider adults, because that’s the message that has been given to us to comment on. But it was helpful, I think, to have the pediatric issue addressed, if ever so briefly.

You have two more questions. I hope they are brief.

DR. HUDGENS: My second question is about safety and the possible association between Q-Pan H5N1 vaccination and the pIMDs. In the slide A-49 this morning, when the integrated safety data was presented -- the large one, ISS-

2 -- the conclusion there was that numerical imbalances for pIMDs persisted. That seemed to me perhaps to contradict the briefing document we were given, which concluded the section on the ISS-2 data by suggesting that there was no association between vaccination and risk of pIMD. So I'm seeking some clarification on this apparent discrepancy.

DR. ARELLANO: You are right, there's a little bit of a contradiction. The numerical imbalance for pIMDs was observed in ISS-1 with H5. There were more cases -- there was still a numerical imbalance, but it wasn't statistically significant -- in the ISS-2.

I also would like to highlight the fact that there are epidemiological studies, as I showed, with a cohort of 1 million vaccinated in Stockholm. They didn't show any association between vaccination and autoimmune diseases.

But you're right, it's a little bit contradictory.

DR. HUDGENS: My third question is about 035, the relative efficacy study, which I thought was really interesting and it hasn't been discussed much today. This gets a little bit at the third question and Dr. McInnes' comment earlier about bridging -- or "inference" is the terminology that's being used -- bridging efficacy from one study to another.

It seems to me that, especially in the presence of the adjuvant, which makes this maybe different than the 2007 discussion -- which I was not part of -- data like the 035 relative efficacy study are really interesting and perhaps the closest to what the efficacy of the Q-Pan H5N1 would be.

I was hoping for just a little bit more discussion about that study. Why wasn't there a control arm? That's one question. Why were there so few endpoints? For an efficacy study, it seemed to be quite underpowered. I think at the end of the day you had 20 endpoints.

Finally, do you think it would be feasible to do something like this if and when we have an H5N1 pandemic.

MS. BOYCE: I'll have Dr. Innis address this one.

DR. INNIS: There was no control group because if it was a pandemic, it would be unethical to have children not offered the benefit of vaccine in a study. That's why we used an investigational vaccine that was really a surrogate for the available vaccine in the United States, which was a plain antigen, 15 micrograms. The relative paucity of cases reflects -- in the communities where this study was conducted, there was continuous transmission of H5N1. We assume that the relatively limited number of cases reflects the fact that the control arm decreased the

risk overall and what we're looking at is the incremental decrease in risk afforded by the addition of adjuvant.

If I could project slide E35.

I just want to remind the committee -- and this is a slide that was shown last February -- what you are looking at in green are data taken from Q-Pan H1N1 studies. The dark color is younger adults. The light color is older adults. The orange is adults, H5N1. The yellow color is elderly individuals.

What we are trying to illustrate here -- H1N1 vaccine is given as a single dose and Q-Pan H5N1 is given as two doses. But at the end of the vaccination course, the age-specific seroconversion rates are approximately equal and the post-vaccination GMTs are approximately equal. If we believe that the specific activity of HI antibody in a population is roughly equivalent if you are measuring it against the threat strain, then this would suggest that these two vaccines, when given with the appropriate vaccination course, will offer comparable levels of protection.

That's a stretch, because we haven't verified in studies how much HI antibody is required to offer 50 percent projection against these viruses. All that we know is that 50 years ago in England, people showed that against H2N2 and against H3N2, 1 to 40 titers were about the mark

of 50 percent protection.

DR. DAUM: Thank you. Dr. Levandowski.

DR. LEVANDOWSKI: I would just like to make the same comment -- could you leave the slide up, please, E35, GSK's slide E35? I just want to make the same comment that I did earlier this year about this kind of comparison. As I understood from a question I asked in February, the H1N1 serologies were done with an HI system using chicken red blood cells and the H5N1 serologies were done with a system using horse red blood cells. Those two really aren't comparable. What would be a fairer test here would be to have both of the antigens tested with the same system, either chick red blood cells or horse red blood cells. But it should be two different sets of slides, really, in my estimation.

The other thing about the 1-to-40 that was just mentioned from the Hobson study that was published back in the 1970s that we all look at and quote because it has some nice information in it -- they didn't actually use a 1-to-40 cutoff. They talked about even lower-cutoff titers as being relevant for protection from infection in a system where individuals who has preexisting antibodies were challenged with a virus in a very well-controlled setting.

That's it.

DR. DAUM: Thank you. Did you want to respond to

that?

DR. INNIS: I do. For those of you that aren't familiar with hemagglutination inhibition assays, the crux of the assay is to standardize the amount of hemagglutinin antigen that is introduced into each well. The way that's done is that you use the specific batch of red cells that are going to indicate either hemagglutination or the absence of hemagglutination in the presence of antibody, and you back-titrate and develop what amount of antigen gives four hemagglutinin units, in our particular test. Others use eight hemagglutinin units.

So whether you use horse cells or chick cells or human cells -- and those are all possibilities -- the test is standardized by protocol to use four units with the specific red cell system. So I do think that this test is an appropriate way to look at inter-subtype --

DR. DAUM: Thank you very much. Dr. Levandowski, do you want to respond to that or not?

DR. LEVANDOWSKI: We'll have to agree to disagree. I actually don't think that the system is fair, to use different red blood cells for trying to make a -- in fact, the sera should all be run together in one test. If you really want to make the comparisons, it should all be done at the same time with same lot of cells, because there can be variation from day to day for the red blood cells,

whether they come from chick or from horse. The horse matters. Different horses have different -- there's a variability in the amount of hemagglutination you see with horse red cells, even for the H5 strains. There can be other kinds of operator variability that goes on.

I'll shut up. But you get the point.

DR. DAUM: Thank you very much for your comment.

I have Dr. Brady. Then we're going to take a five-minute break and then we're going to deal directly with the questions that were posed.

DR. BRADY: My question relates to administration of the vaccine. You presented the data that shows the benefit of having two doses. But how was the duration between the two doses determined? Were there any findings that looked at, if the duration is less than or greater than 21 days, how that affects the response?

MS. BOYCE: Dr. Innis will comment on the dosing regimen.

DR. INNIS: Just to remind you, the licensed vaccine administers two doses with a 28-day interval. We sought to decrease that and settled on 21 days.

Slide up.

We did do a study after the Phase III study was completed to explore the immunogenicity of accelerated dosing. What you are looking at here are geometric mean

titers -- and we have also denoted the seroconversion rate -- of four groups of subjects. Subjects were allocated to these four schedules randomly. These are healthy adults 18 to 64 years of age. The highest responses were seen with the 21-day schedule. The response diminished, in terms of GMT, by about 50 percent with the 0-14 schedule, but still had a 93 percent seroconversion rate. Seven days was not different from giving two doses in individual extremities at day 0. That also resulted in acceptable immune responses. So it is possible to make this a single-day immunization. You have to give the subject two doses, one in each arm.

This is not part of the application. This was submitted as supportive data only.

DR. DAUM: Well, it’s appropriate to maybe consider it during the free-association phase of our deliberations this afternoon.

We are now going to take a five-minute -- literally -- break. I have 2:45. We meet again at 2:50. We will consider the first two questions and then the discussion points, and try to end on time. Thank you.

(Brief recess)

DR. DAUM: We are now in discussion aimed at the committee’s first question for consideration today. I put it on the screen for you to consider once again. If there

are discussion points to have about this, let’s have them. As soon as the discussion wanes or gets repetitive, we’ll go to a vote.

Again, I would like to hear from all committee members on these subjects. Let’s go.

DR. DUBOVSKY: The indication for this vaccine is to be used during a pandemic, controlled by the government. In that case I think we need to consider the benefit-risk of that in the context of illness, which seems to have a 60 percent case fatality rate. So when we think about this and when you guys deliberate on it, it should be with the thought that the vaccine is going to be used in a timely fashion by the people who understand what’s going on in the community, and that the risks which may or may not eventually be proven to be associated with this vaccine are real.

DR. DAUM: That’s a helpful comment, but it’s not really focused on this question. While you have the microphone and the floor -- and I know you don't vote -- I would like to hear your comments on what you think of this question.

DR. DUBOVSKY: The immune responses for inactivated vaccines have a long history. I think we have pointed out many of the issues around these. I think the sponsor has done what they can to satisfy the requirements,

and they have done so.

DR. DAUM: Other comments related to this question? Dr. Levandowski.

DR. LEVANDOWSKI: Let me just clarify what I'm trying to say. In spite of what you heard me saying just a few minutes ago, I agree that the sponsor has done a very nice job of demonstrating the immunogenicity of their vaccine product, in the context of what they are showing us with the added adjuvant as compared to their unadjuvanted vaccine. Generally, I would say they have done the best you can.

I would also say that I don't think it needs to be in the context of any other product. I think what data they have stand on their own for the vaccines that they are making.

DR. DAUM: That comment is aimed at this question. Dr. Wharton.

DR. WHARTON: I believe that the data presented do support the use of the vaccine in the context of prevention of H5N1. Of course, there are uncertainties about all of this, but based on the known science, this is what we can do, and I think the sponsor has done a good job of it. It's a strong case.

DR. DAUM: More comments on this question? Dr. Cheung.

DR. CHEUNG: When I was looking at the data, I was struck by the high mortality associated with -- given that the antigen by itself is not as efficacious and it seems like the adjuvant really marked improved the immunogenicity. The immunogenicity would be enhanced significantly by the adjuvant. Given the fact that in the case of an epidemic or pandemic, there is a high mortality and that the immunogenicity data seems to be very convincing -- obviously there’s no way to evaluate the efficacy unless there is an outbreak. But it seems like the proxy, using the H1N1, is a reasonable approach.

Again, looking at the risk-to-benefit ratio -- I know there’s a second question -- in terms of risk, there are the immediate side effects, which I believe are fairly minimal, and then there is a short-term side effect in terms of narcolepsy and inflammatory diseases. The incidence of those is quite low. Given that the sample size for the vaccine group is almost six times higher than the control, I’m curious whether those numbers actually reflect the normal population. I didn’t see all the data on that. I presume that is likely to be due to sample size, in terms of the side effects.

So overall I’m very comfortable with the benefit-to-risk ratio in terms of giving a yes vote.

DR. DAUM: We’re not requesting votes at this

time. We're requesting comments that go to issues that might help you decide how to vote.

Dr. Air.

DR. AIR: I'm absolutely with Roland Levandowski. We do not know what these HA titers mean in terms of protection. It's dangerous to speculate.

But on the other hand, what the sponsors have clearly done is to demonstrate that this is immunogenic, and some antibodies are going to be better than no antibodies. I think they have demonstrated immunogenicity.

DR. DAUM: Thank you, Dr. Air. Dr. Piedra.

DR. PIEDRA: I think GSK has demonstrated and met the CBER definition for immunogenicity for the two-dose. I would only like to raise the issue that, although this is not what we're discussing here, many individuals during a pandemic may only get one dose. One needs to think about, maybe down the road, how one can do better than a two-dose requirement. Unfortunately, like the 2009 H1N1 pandemic, it came late and we were not able to give two doses to the majority of children or individuals during the major peak.

DR. DAUM: I think what you're sort of saying that bears on this question is the immunogenicity data means that two-dose data, if I can put words in your mouth.

DR. PIEDRA: Correct. It's the two doses that have met the requirement. One dose has not.

DR. DAUM: Other comments that bear directly on this question? Dr. Gellin.

DR. GELLIN: A couple of things. To clarify the language, this question talks about increased risk of exposure. The proposed indication is exposure to influenza A virus/H5N1 subtype -- whether or not we need to worry about that. I guess I'm not sure what a subtype is and whether or not this is for all H5s or what. I think we just need to clarify, because there's some asymmetry between this question and the proposed indication.

DR. DAUM: I think we should ask the agency what they meant by the question, vis-à-vis your question. Dr. Weir.

DR. WEIR: I think the way it's written and it's being asked is, is it specific for this particular strain that is being licensed? If you remember the slides that were presented earlier today, once licensed, then strain changes can be effected to change the actual strain of H5 that's used in the vaccine.

DR. GELLIN: So for this particular strain, when you look at the dendrogram, this particular strain has lots of progeny pretty quickly. The degree to which there is some cross-protection -- whether that's an expectation or whether or not this exact molecular strain is the one that has to come through town.

DR. DAUM: In a way, that’s a separate question. It’s not really the question that the agency has asked us to deal with.

DR. GELLIN: It’s just a clarification of this one. Then I have a second comment afterwards.

DR. DAUM: I think you have had your clarification, unless I misunderstood something. Go ahead with your second question.

DR. GELLIN: The adults at increased risk of exposure -- there have been requests -- and others may want to speak to this -- by laboratorians. I think that there is this issue now: Is it only going to stay in the stockpile or are there people now who are at increased risk of exposure who would want some protection?

DR. GRUBER: I’ll let GSK also comment on it. But, Bruce, it really is both. It’s for use in adults during a pandemic. But we did not exclude situations like you mentioned a minute ago -- laboratory workers working with the H5N1 virus. There may be benefit for these persons to receive the vaccine. That’s what we had in mind when we said “at increased risk of exposure.”

MS. BOYCE: The vaccine will be under the control of the US government. They will determine the use of the vaccine. I don't know if Dr. Robinson wants to comment.

DR. DAUM: I don't know if he does either, but he’s welcome to say no.

DR. ROBINSON: As is indicated, the risk of exposure for those laboratorians, those individuals who may be going into areas where they may be at risk in foreign countries, and during a pandemic.

It is a brisk discussion that we have had over the past eight months within the Department. A paper is going to be hopefully submitted talking about the challenges of this and hopefully will move into a public forum for the discussion. But right now this is what I think we’re all comfortable with.

DR. DAUM: Having said that, unless there are other burning issues, I think we’re ready to vote on this first question.

Do you have a comment?

DR. BENNINK: Just one to GSK. Were your production people immunized with this in part of the trials?

MS. BOYCE: No.

DR. DAUM: Okay, I’m going to move forward to asking the committee to vote. I think we’ve heard from pretty much everybody in terms of how they feel about this. Obviously nothing is perfect. We have a lot of information. We don't have every little thing that we

would like to have. But we have a question that we need to answer.

The question is: Do the immunogenicity data support licensure of Q-Pan H5N1 for use in adults at increased risk of exposure or during a pandemic?

I'm going to ask now that people vote. We do it electronically. We have little buttons in front of us that say yes, no, or abstain. We do it all at once, and then the results will be shown on the screen.

(The vote was taken.)

MR. JEHN: The vote is unanimous, 14 yeses, zero noes, and zero abstentions. For the record, I need to read the names.

Dr. Gellin was a yes. Dr. Cheung was a yes. Dr. Hudgens was a yes. Dr. Air, yes. Dr. Tacket, yes. Dr. Gray, yes. Dr. Levandowski, yes. Dr. Bennink, yes. Dr. Piedra, yes. Dr. Marcuse, yes. Dr. Wharton, yes. Dr. McInnes, yes. Dr. Brady, yes. Dr. Daum, yes.

Does the industry rep want to have any comment?

DR. DAUM: I think he did.

MR. JEHN: Yes, he already did.

DR. DAUM: The first question is done. I must confess to liking the old way, when we said our yeses and noes ourselves. But here we are in the modern era.

So let's go on to the second question. This is a

variant on the first, but a very important variant. Do the safety data support licensure? The rest is the same.

I would like to have a discussion first among committee members, if there is any, focused on this question. Then we'll put it to a vote. Then we'll discuss the, I think, more difficult third question.

Does anyone have any points they wish to raise or discuss? Dr. Gellin.

DR. GELLIN: I guess the question is whether or not we have seen the full experience that GSK has with this adjuvant. Maybe we have.

A related question is whether or not there is a seasonal adjuvant that is actually in the pipeline.

Those are tangential questions, trying to get to the point of how or when there might be more data on these rare but concerning adverse events.

DR. DAUM: But this is a good time to ask questions like that. We'll call on Ms. Boyce to lead us through the company's response.

MS. BOYCE: At the current time there's no seasonal adjuvanted vaccine in the pipeline.

Are you asking a question about experience with AS03 adjuvant vaccines? You asked for the complete experience? You want post-marketing, clinical trials, or everything?

DR. GELLIN: High level.

DR. DAUM: I think we would like to very briefly hear how else you are using this adjuvant.

DR. ARELLANO: AS03 is used with Q-Pan and D-Pan. You have seen everything that we have, as far as I'm concerned.

DR. INNIS: This is not part of the briefing document, because it's not a pandemic vaccine, but we did develop and take through Phase III a trivalent vaccine with AS03-B that was administered to 43,000 adults over the age of 65. This trial did not meet its primary objective of establishing superior protection in a relative efficacy trial. But there were extensive safety analyses.

With respect to diseases of potentially immune-mediated origin, there was no signal emanating from this trial that they were increased in those who received the adjuvanted formulation relative to those who received the unadjuvanted Fluarix formulation.

DR. DAUM: Thank you very much. Does the sponsor have one more comment?

DR. WETTENDORFF: I just want to make one small comment. We are considering the AS03 adjuvant in some of our projects which are in early development. There might be more experience with a AS03-adjuvanted vaccine, non-flu, in the future.

DR. DAUM: Thank you. Dr. Bennink.

DR. BENNINK: I'll go back to this, in terms of the transplantation or even the autoimmune hepatitis that there were some comments about in the report. In the 43,000 that you were talking about or in any of the other studies, even with the pandemic H1N1 that was done, you are completely comfortable, if you will -- or even beyond that -- that there is no concern that those will be seen in terms of things with the adjuvant?

DR. ARELLANO: Let's talk first about the autoimmune hepatitis issue, which is slide S-15, please.

This is the experience with the two reports in clinical trials. The first one is with Q-Pan H5N1. This is a 29-year-old male. Three autoimmune experts considered diagnosis doubtful, and possibly nonspecific reactive hepatitis, probably a prevalent disease.

For D-Pan H5N1, there was a 3.5-year-old female with probably autoimmune hepatitis prevalent. I am reading directly: Both CHMP and a panel of external experts concluded that the evidence did not support a causal association between AS03-adjuvanted vaccines and autoimmune hepatitis.

The next slide, please.

This is the experience with postmarketing data on D-Pan, on Pandemrix. We have received, with 31 million

doses administered, five spontaneous reports. Assuming that there is significant underreporting of spontaneous reports, even with that, they are well below the expected background incidence rate, which is 1 to 2 cases per 100,000 person-years. Some of the details of the cases are here.

I hope this puts the whole issue into appropriate context.

With respect to the transplant rejection, slide S39, probably one of the epidemiologists should comment on this. Go ahead.

DR. COHET: Catherine Cohet, epidemiology.

This is a summary of observational studies we are aware of which have been published so far on transplant patients. We saw mostly reports of case series of a cohort of vaccinated transplant recipients who have been followed over time. There are ten studies here. In one study -- this is the Meyer reference -- there were two cases of rejection. However, this study was not controlled, so it’s difficult, without a comparison group, to make any conclusion.

In another study -- this is the Katerinis reference -- there were transient increases in anti-HLA antibody, but this does not translate into any clinical rejection.

Finally -- this is the Schaffer 2011 reference -- there were some small increases in cellular rejection, which were not persistent over time.

However, the majority of observational data so far shows no issues with clinical rejection. This data is overall reassuring.

To go back to the question asked this morning, no events of transplant rejections have been reported in clinical trials of Q-Pan H5N1.

DR. DAUM: With respect to your last comment, I wonder how often patients who are transplant recipients were actually enrolled in your clinical trials. Were they excluded or enrolled?

DR. INNIS: That would have been up to the investigators. If someone had an immune deficiency condition, they were excluded from the large safety study, 002. But if they were a graft recipient and had stable medications and no adverse event within 30 days of enrollment, they would have been eligible. I don't know if there were any solid organ transplantees in the program.

DR. DAUM: Thank you. Could we have the question back up again?

Other comments about safety? Dr. Piedra.

DR. PIEDRA: This will be more mundane type of safety. I did not hear the general kinetics and timing of

the acute local reactogenicity -- for instance, pain. Does it occur immediately after injection? Does it last three, four, five, six days?

That will be the first one.

DR. DAUM: Does the sponsor wish to address that?

DR. ARELLANO: I apologize, I still have difficulty hearing. Your question is about the onset of pain and the duration of pain?

DR. PIEDRA: Correct.

DR. ARELLANO: The median duration of pain was three days. Ninety percent of the patients stopped having pain by day 5.

DR. PIEDRA: As a follow-up, there was a small percentage that had severe pain. Did any of those miss work? Was the pain severe enough to miss work or miss school?

DR. ARELLANO: Do you remember, Bruce? I don't.

DR. INNIS: We didn’t specifically collect that data, but grade 3 pain implies that there was interference with activities of daily living, such as attending school or missing work.

Could we put the slide up?

You can see the actual histogram of grade 3 pain. It’s focused in the first half of the week of follow-up. But there are a small number of individuals -- .1 percent,

for instance, on day 3, .1 percent severe pain. Most of the pain is acute and immediate.

DR. DAUM: Thank you. Dr. James.

DR. JAMES: I did present those data in my slides. The definition of severe pain is “prevented normal activity.” Specifically it says school or work. Presumably, that means, if they had severe, grade 3 pain, they could not work and they could not go to school.

DR. DAUM: I have a question for FDA. Do you wish us to deal with this question as it is, in the sense that H5N1 vaccine would be used during a very serious pandemic to deal with a disease with high mortality? In which case we might be a little less sticklers about safety than in a general comparison. Or do you want us to answer it in general about comparing vaccine A to B, irrespective of their planned use?

DR. GRUBER: We would like for you to answer and vote on these questions in the context of this product being used during a pandemic.

DR. DAUM: Thank you. I thought that’s what you would say, but I wanted to be sure. I think it’s important.

Other comments about the safety question before we vote on it?

(No response)

In the absence of hands up, I think we're ready to vote on it. This is your time. Yes, no, or abstain. Then, magically, Don will calculate how we vote.

(The vote was taken.)

MR. JEHN: Again we have a vote of 14 yeses, unanimously, zero noes, and zero abstentions.

For the record, Dr. Gellin was a yes. Dr. Cheung was a yes. Dr. Hudgens was a yes. Dr. Air, yes. Dr. Tacket, yes. Dr. Gray, yes. Dr. Levandowski, yes. Dr. Bennink, yes. Dr. Piedra, yes. Dr. Marcuse, yes. Dr. Wharton, yes. Dr. McInnes, yes. Dr. Brady, yes. Dr. Daum, yes.

DR. DAUM: We now move on to the discussion items. Dr. McInnes, I warn you that I would like you to lead off this discussion, if you don't mind.

Please discuss the following two approaches to confirm the effectiveness for traditional approval. One is to confirm the clinical benefit of Q-Pan with efficacy data generated with the US-licensed seasonal Fluvax virus vaccine made according to the same process. Two is to confirm the clinical benefit of Q-Pan by conducting an effectiveness study during an H5N1 pandemic.

We have heard multiple comments that sort of indirectly bear on this, but now we'll deal with it directly.

Dr. McInnes, would you comment, to start?

DR. MCINNES: I think I've made my comment earlier. I would like to hear what other people have to say.

DR. DAUM: If I can just repeat it, your comment is that you're not sure that we need to deal with this question and can leave it as an accelerated approval. We won't say anything else about it right now, and just let other people say what they will. Dr. Wharton.

DR. WHARTON: Given where we are with this, I'm comfortable with efficacy data derived from a study of a US-licensed seasonal influenza virus vaccine made according to the same manufacturing process, option 1 on the slide above. I believe that's what can be done. This is, I think, a pragmatic approach that the committee has taken during previous discussions of this same topic.

I understand that there are a number of inferences that have to be made to accept that line of reasoning, but I think that's what we can do and that that will provide a good deal of information that will support additional confidence in the product.

Obviously there will still be uncertainty. Clearly everyone will want data during an event, should it be necessary to use a vaccine of this type. I think the sorts of systems that Dr. Bresee described earlier in the

presentation can provide enormously helpful data if we are able to do that during a pandemic event, which I hope we would. That’s certainly what we plan to do.

But I don't think we can necessarily count on having manufacturer-specific data, and given that, I think what we’re left with is the first option.

DR. DAUM: Thank you. Dr. Air.

DR. AIR: My problem is the second word. It says “to confirm” the clinical benefit. To my mind, you can only do that with an experiment. You can’t take data from a completely different experiment. So I would to go with number 1. I prefer number 2.

DR. DAUM: With regard to point number 2, I heard several comments this morning about the feasibility of number 2. I heard them from several people. Maybe they would be willing to come forward. We could call on them if they are not.

Is it feasible, if there’s an outbreak of H5N1, to conduct an effectiveness study during that? Is this a conversation that’s going to lead to something meaningful? Comments on that, please. Dr. Piedra, then Dr. Wharton.

DR. PIEDRA: I think the 2009 pandemic is an example. One can see that if vaccines are received late into the pandemic, it’s going to be difficult to reliably confirm the clinical benefit. A good example is the three

studies that were available in Canada that FDA is not using to confirm, but it’s using to at least collaborate the confirmation of efficacy.

I think during a mild pandemic, it was difficult, at best, to confirm, with number 2, and during a moderate to severe pandemic, I think it’s unrealistic.

DR. DAUM: That’s an important point. I have Dr. Wharton, Dr. Gellin, and Dr. Bennink.

DR. WHARTON: Just to reiterate the point, during the 2009-2010, the effectiveness data which were derived in the observational studies done during the pandemic did not provide manufacturer-specific estimates.

DR. DAUM: That’s an important point. Are you suggesting that that would be a very sticky hurdle to cross?

DR. WHARTON: I think it would be an extraordinarily difficult thing to do -- not necessarily impossible, but very, very challenging. To require that the sponsor do that in the course of a pandemic, which I believe is what the accelerated approval actually requires, I think would be extraordinarily difficult.

DR. GELLIN: A couple of things. We have gone two-thirds of the day about flu and haven’t mentioned the word “unpredictable” yet. I want to make sure we inject that into this, because I think the issue is that there

will be surprises, and who knows what we'll see? And the degree to which anything done before is predicting what happens later -- I think we just have to keep that in mind. The strain may not be exactly the one that we're aiming at. It may be slightly different. We want to keep that in mind.

The other one is that I think we need to keep expectations in our mind as well. The idea that you are going to do an effectiveness study in the middle of a pandemic -- I think we can discuss whether or not that can be done and where it could be done. Other countries may have a single vaccine in their country. Some of those studies may be done, and their generalizability we will have to discuss.

But just because you're doing a study doesn't mean you are going to have an instant answer. I think it will be a long time until there's an answer about effectiveness if a study is done in the middle of a pandemic.

But we could hear from the company about what their plans are, or what other regulators in other countries have thought about or considered as far as doing efficacy studies in a pandemic. My sense is that many countries may have a single supplier for a pandemic vaccine.

DR. DAUM: I think calling on the sponsor before we go to the next speaker is a good idea.

Ms. Boyce, you have been jumping up to the microphone for other issues, but I don't notice you up there for this one.

I think someone from the company this morning commented that a post-licensure effectiveness study during a pandemic would be extraordinarily difficult. I think we could hear from you as to why that is so.

DR. INNIS: My personal opinion is that it’s not possible to demonstrate the effectiveness -- if this country were to deploy Q-Pan in an H5N1 outbreak, it would be one of several vaccines deployed. For the foreseeable future, it would not be possible to generate product-specific estimates of effectiveness.

However, GSK does hold a contract with Health Canada. This contract is midway through its evolution. I don't know if it will be renewed in the future. But if in the next several years Q-Pan is deployed in Canada, it will likely comprise the bulk of doses that are used in Canada. You saw examples of what Health Canada, through its provincial agencies, was able to do. We would be willing and would try to collaborate with Health Canada to generate data.

When we approached the provincial agencies to

have access to the source data so that it could be reviewed by the FDA, two of the three provincial health agencies were not able to make that data available to us.

There are two issues. One is, can a study be done? Secondly, could the data be made available for review?

So Canada is perhaps a partial solution.

DR. DAUM: Are you currently licensed there? Will you be the only vaccine licensed there? Tell us why it's better in Canada.

DR. INNIS: We have an application that's under review. The action date is coming up in several months.

Why is it better in Canada? Canada has a contract with GSK. We make pandemic vaccines for them. And they have a unified health-care system, of course, that's different from the United States.

DR. DAUM: How does the agency feel about an effectiveness trial done in Canada?

DR. GRUBER: If you remember the discussion in February, that was actually one option at that time, option B, that was on the table. The effectiveness study referred to, the Van Buynder study, was a study conducted in Canada. We at that time decided we would be willing to review the data. As Bruce mentioned, there were actually three studies. Only from one study could GSK get the raw data

for us to review. But you saw what the outcome was. We did not accept the data, although it suggested effectiveness of H1N1 AS03 vaccine. We did not accept it to support traditional approval because of study limitations.

So we would not exclude entertaining effectiveness data from other countries, but there are limitations. We had one example with the Van Buynder study that we did not accept.

DR. DAUM: One of the issues that I recall there was that you weren't involved in the design of that study. There were several other issues as well. Would that help?

DR. GRUBER: And neither was GSK. There were several limitations as to why we did not think that that study could support a traditional approval or could be taken to confirm the clinical benefit of the H5N1 candidate vaccine.

DR. DAUM: Dr. James, I'm going to let you go out of turn, because you're the agency, after all. Then Dr. Bennink and Dr. Marcuse are next.

DR. JAMES: I just want to clarify, since I present the fact that GSK did not participate in the conduct and FDA did not participate in the design of the Arepanrix H1N1 study, I did not cite those things as specific limitations. There were limitations to the study,

but I just wanted the committee to know that we did not participate in the conduct and design of the study.

DR. DAUM: And I didn't mean to imply that that was a limitation, but I thought it would have been more likely -- maybe I'm wrong -- that the agency would have accepted the results if they had been involved in the design. Perhaps not.

DR. JAMES: No. The agency does accept studies that are conducted out of the United States in which we have not participated. Obviously there's a higher risk of not accepting a study or there being issues in the study that we could have assisted with. But we do accept studies out of the country and studies that we have not participated in the design of.

DR. DAUM: Before I call on Dr. Bennink, I just want to admonish everybody on the committee that I would like to hear from everyone with respect to this question. If you haven't made a comment, you do run the risk of my calling on you to make one.

Dr. Bennink.

DR. BENNINK: I just really want to reiterate what was said before. One of the biggest problems that I see in terms of looking at efficacy or effectiveness is really the fact of the influenza drift. If you wait a long time, if it's not used for five, six, seven, eight years or

whatever, if the HA changes significantly more in terms of jumping to be able to transmit in people extremely well, it could be quite different. Yet you have a stockpile that may be somewhat effective or that you think is at least usable in some ways, and you may use it. So then it becomes difficult in terms of trying to do some of the efficacy stuff later.

The other thing is that some of the data that we have seen, even from the Canadian study -- you have seen enormously high numbers of effectiveness, 100 percent in many of these cases. I don't think people consider the flu vaccines today to be anywhere close to that. That’s something that is, I think, quite a ways out from what reality probably is.

DR. DAUM: Could I admonish again everybody in the room to tame your electronic devices so that they don't make noise or distract from this discussion? I would really appreciate that.

Dr. Marcuse.

DR. MARCUSE: Multiple people have alluded to the virtual impossibility of doing a manufacturer-specific efficacy trial in the face of the pandemic, and I appreciate that.

I’m going back to the question I asked Dr. Bresee earlier today. While I recognize that there are formidable

barriers to doing a manufacturer-specific efficacy trial of seasonal vaccines, I'm not convinced that they can't be overcome. Because of what we're discussing today about the subtleties of slight differences in manufacturing processes or antigens or in adjuvants, carrying out manufacturer-specific efficacy trials with seasonal vaccines would seem to be me to be a wise investment to inform future discussions of this committee.

DR. DAUM: Is Dr. Bresee still here? Do you want to comment? Your name was taken in vain during that question -- or at least it was taken. Let's put it that way.

DR. BRESEE: I would just say that I think that it's possible to do manufacturer-specific estimates, conceptually at least. My comments this morning were directed at the fact that the current systems -- while they may generate those some years or may have the capability of generating those some years, we certainly can't guarantee that they would generate those during a pandemic, for all the reasons that have been mentioned here.

I don't think it's beyond the realm of possibility that one could invest in a system that would collect those data and be closer to guaranteeing that. But with the current system we have, I'm afraid we just can't do that.

DR. DAUM: If this committee decided that approach number 2 was more desirable and you dealt with Dr. McInnes' concern that 1 or 2 is necessary -- but let's say they are, and let's say number 2 is more desirable -- where would you ask the agency to put pressure on, you or the manufacturer, or both, to do the study and try to do it to the very best of one's ability? I recognize that if there's an H5 pandemic, there's going to be bedlam in this country. Nevertheless, we're asking about feasibility now.

DR. BRESEE: I think this is probably above my pay grade. But I would say that if the US government were to design such a system, a collaboration between FDA and CDC, at least -- FDA, CDC, and NIH as sort of a cross-agency collaboration -- could think of a way to do this.

DR. DAUM: I didn't hear the word "manufacturer" in there.

DR. BRESEE: I think we're happy to work with the manufacturers. Our current systems at CDC don't involve manufacturer input or funds, for the reasons you might expect. I think that for an extraordinary situation, engaging manufacturers in the solution would be a good idea. I'm not sure how to do that, but I wouldn't be averse to it either.

DR. DAUM: Go ahead, Dr. Gray.

DR. GRAY: While I realize that there would be

some time delay with respect to getting the vaccine out -- and who knows the course of the movement of the virus? -- we certainly know that in some countries the 2009 pandemic was delayed. I understand the CDC is setting up cohort studies, and perhaps some of those seasonal cohorts, where they are expecting to look at seasonal vaccine, could be employed in a setting where it was delayed.

But in the United States, I think we could look at occupational groups that we would think would be priority to get the H5N1 vaccine. In some sort of effectiveness study we might be able to compare their experience with similar people, say age- and sex-adjusted, without those occupations. I'm thinking of responders, if it affected poultry, health-care workers, and particularly the military. At least in the recent prioritization in 2007 or 2006, the military was thought to be a priority group.

So there might be a way to do it, in a limited way, with people who are going to receive the vaccine as a priority, and looking at effectiveness.

DR. DAUM: Thank you.

One question before we go on. Does the accelerated approval approach necessitate an attempt to get to the traditional approach as an endpoint? Are we choosing between 1 and 2 as it has to be done of them or

could we leave it as an accelerated approval and let the chips fall where they may?

I would like to ask the agency to comment on that.

DR. GRUBER: As I stated before, the accelerated approval provisions do require that an applicant verify and describe the clinical benefit of the vaccine further. The regulations also state that the studies need to be adequate and well controlled, and the applicant has to perform these studies with due diligence.

This is what the regulations specify. There is always the -- if you say, okay, we'll lean towards 2, of course, you have the safety and immunogenicity data for the vaccine at the time of licensure. But you have to realize that the applicant would perhaps never be able to really then confirm or verify and describe the clinical benefit of this vaccine further because of the limitations that we have all heard about today, given what is currently doable.

I want to take this a little bit further. And I'm not saying this is what's going to happen. There is some discretion. But the regulations also go further -- and, Bruce, I brought the regulations with me again -- to say that you could even withdraw the licensure of a product if this is not followed through and these confirmatory studies are not conducted.

Now, is that a likely scenario for a pandemic flu vaccine? I think that is probably unlikely. But again there is this requirement to do what's feasible to verify and describe the clinical benefit of the product.

DR. DAUM: Could I bug you for a follow-up question?

DR. GRUBER: Sure.

DR. DAUM: We just picked on Dr. Bresee and asked him whether CDC could lead or design -- or whatever the right word is -- prepare themselves somehow for an effectiveness study, should a pandemic occur -- or when it occurs. I don't know which is the right way to say it. I asked whether the sponsor would be involved in such a design. I believe he said that of course they would.

My question for you is, would FDA accept a study like that that they participated in the design of, presumably, and approved of the design, between CDC, the sponsor, and FDA?

I just would like to explore this with you, because I'm not sure that, if we leave it that option 2 is preferable and we want the company to just go it on their own, we're going get much. So this question is, would this modified approach be okay?

DR. GRUBER: Here we are really stepping into these regulatory nuances. I think what the agency would

accept is, if we go with option 1 -- to confirm the clinical benefit with efficacy data generated with a US-licensed seasonal influenza vaccine -- for the company then to make a commitment to collaborate with government agencies to further evaluate the effectiveness of the product. During a pandemic, this is something that we would accept.

But, of course, the latter would not be a requirement in the regulatory sense. Number 2 really will take number 1 off the table. Number 2 really means to require the applicant to conduct a study. The regulations really spell out that it’s the applicant.

Again, there are different views within the FDA on how you can interpret that. I should be fair to say that. But I see it really as an obligation of the sponsor to conduct the study with due diligence. That is very different from the scenario that I just described and that is spelled out in our guidance, which is for the company to agree to collaborate with the government in during a pandemic.

DR. DAUM: Could the company comment on Dr. Gruber’s remarks? I heard what sounds like a plausible route toward dealing with this issue. That would be a collaboration between CDC, FDA, and GlaxoSmithKline. But it sounds like there still would be a burden to take this

into possibility number 2, should a pandemic occur. We all hope it doesn't occur, but should it occur. Do you accept that challenge?

DR. INNIS: As we stated this morning, the company would willingly and gladly collaborate with the US government in a government-sponsored study to examine the effectiveness and the safety of Q-Pan H5N1, should it be deployed in this country. The challenge, for us and for the government, would be to ensure that there is a platform able to execute such a study in the place where the vaccine will be used and that we have a system that would allow us in retrospect, once cases and controls are identified, to accurately know whether people got no dose, one dose, or two doses of the product.

Yes, we want to do that.

DR. DAUM: And would accept the due diligence of doing it as part of the --

DR. INNIS: Well, due diligence is a different issue.

DR. DAUM: No. It's the issue I'm asking about.

DR. INNIS: A commitment in the regulatory sense that we must continuously attempt to do such a thing --

DR. DAUM: In collaboration.

DR. INNIS: Collaboration, yes.

DR. DAUM: You must continue to do such a thing,

but in collaboration.

DR. INNIS: In collaboration, should a pandemic arise and the vaccine be deployed, yes.

DR. DAUM: Okay. Dr. James.

DR. JAMES: Just to give a little more context to the question, I think Dr. Daum you asked if a product could be approved and left at accelerated approval. Though it’s a very different example, a very different situation, in the Center for Drugs, this sort of process was taken with cipro and levofloxacin, or Levaquin -- it’s actually the two brand-name drugs -- during the anthrax situations, where both of them were approved under the accelerated approval provisions. For cipro, their requirement was to cooperate with the government in the event of an attack. During the anthrax attacks of 2001, the government conducted the study, without any input from the company. They were excused, and the government conducted the study. That study went forward to support traditional approval of ciprofloxacin.

The other example is the Levaquin example, where that drug was given accelerated approval for the same indication, but it was done in 2004, I believe. There have been no anthrax attacks since then. That drug remains under accelerated approval for post-exposure prophylaxis to anthrax.

Again, those are drugs and these are vaccines that we're talking about, H5N1 -- apples and oranges in the sense of what the entity is. But in terms of regulation and in terms of FDA products staying under accelerated approval, we do have precedents.

DR. DAUM: Thank you. I found those comments very helpful, Dr. James. Thank you.

Dr. Gruber.

DR. GRUBER: I would like to add to Dr. James' comments. I'm actually very glad that she is bringing up this example of ciprofloxacin for inhalational anthrax in a post-exposure setting, because it illustrates very nicely the unique considerations and challenges that come with every product that we have to license for which it is not easy to do an efficacy study in the classical sense.

I fully agree with Dr. James that these situations -- ciprofloxacin for inhalational anthrax in a post-exposure setting versus a pandemic influenza vaccine used during a pandemic -- are not really comparable. I should add that for the ciprofloxacin approval that, granted, got an accelerated approval, the regulatory action was really based on data and studies from an animal model that closely resembled human disease. In other words, the data set available at the time of licensure was very different. They had this animal model. Therefore, the

requirement to describe and verify the clinical benefit was rated much differently, I would say, because you had the animal model data to really support the accelerated approval decision at that time.

So it’s an example. I don't necessarily think it’s an FDA precedence. It just shows the unique considerations that you have to factor in every approval decision that we’re making.

DR. DAUM: Thank you very much, Dr. Gruber.

DR. DUBOVSKY: In the context of this sort of vaccine for a pandemic, where the government is the sole owner and user of it, I like the flexibility of both approaches. It would allow the tools that Dr. Robinson needs to bring them to bear. On the other hand, I agree that the feasibility of number 2. But if you were to do that, just to be clear, those results would come out after the pandemic is likely to be over, and so you would get confirmation after the product is used. The fact that it’s licensed or not I think is a bit irrelevant.

DR. INNIS: Mr. Chairman, could I point out two other things and perhaps ask Dr. Gruber to make a comment?

My understanding is that under the accelerated approval regulations, in the prescribing information a distinction will be drawn. It will say that this vaccine is licensed on the basis of immune response data only.

There are no clinical data to support its effectiveness --

DR. DAUM: Safety data.

DR. INNIS: Immunogenicity and safety. But there are no data to support its effectiveness. This may have some bearing on how the vaccine is perceived when it is used. So what you decide today makes a difference.

But one other consideration is that the license that’s currently under review is for adults only. At least in our interactions with another vaccine that is under accelerated approval, we were not allowed to extend the indication to children while it was in accelerated-approval status. It is our intention to submit a supplement to this license to extend the indication into children. But I wonder if that would be permitted if we are under accelerated-approval status only.

DR. DAUM: Does the agency want to respond? You don't have to.

DR. GRUBER: I actually have to be honest and say we haven’t really had these types of discussions. But I would like to stress the point that we do not need this discussion if we would think that it is reasonable to confirm the clinical benefit of Q-Pan with efficacy data derived from studies with a seasonal vaccine, because we could then do a traditional approval and we would not have these questions on the table.

DR. DAUM: Thank you.

The comment only may be a little out of phase with events if there’s a pandemic, because presumably we would want to have data about children before the pandemic, because children will be exposed if there is one. I may have misunderstood something, but I don't think you could get to traditional approval without the study -- if we go the route of number 2 -- without a pandemic actually occurring. I’m not sure how that would play out.

I would like to hear from Dr. Tacket, if you wouldn’t mind, on this issue.

DR. TACKET: Option number 2 was the one I originally thought I was interested in, but I’m being swayed by other arguments. One of the benefits of option number 2, in addition to looking at the efficacy during an H5 pandemic, would be to further explore the side effects that we have been talking about with regard to autoimmune disease and narcolepsy. That would be an opportunity that might not exist with option number 1.

I agree with all the comments that have been made about the desirability of option number 2, but with the additional thought that we’ll learn a lot more about these rare but serious side effects that occurred with the vaccine.

DR. DAUM: Dr. Goodman, you had your hand up.

DR. GOODMAN: I was just going to comment about something that may help the committee in thinking about this. As part of the cross-government effort at dealing with emergency preparedness and getting medical countermeasures out there, whether for flu, bioterrorism, whatever, we really are focusing on how we can get the best information in an emergency, how we can build information systems that would allow us to pull out product-specific data, et cetera. If the committee were to vote for number 1, for example, strong confirmatory evidence, that doesn't mean that the government is not going to be working together to get all the efficacy and safety data that we can during a pandemic. We are going to try to do that.

But I think it's important to realize that the present systems have limitations and that we can always prepare for what we believe will happen, but often what happens is different than what we believe. In H1N1, certainly a tremendous effort was made to collect safety data in real time, and that was generally quite successful. Efficacy data is a whole other challenge, but everybody is working together to try to get us better positioned to do that.

DR. DAUM: Thank you. I find those comments very soothing, actually.

Dr. Wharton.

DR. WHARTON: Just to follow up on Dr. Goodman's comments, one of the challenges with studying effectiveness has to do with the clinical disease endpoint. It requires particular kinds of infrastructure to assess that. Monitoring vaccine safety requires documentation on the adverse event and on the type of vaccine administered. In the context of a pandemic, I would have every expectation that both the existing everyday systems we currently have that can capture that vaccine-specific event and whatever additional systems are added on top of them would provide robust systems for monitoring safety. Not committing ourselves to capturing product-specific effectiveness in the context of a pandemic shouldn't be construed that there wouldn't be huge efforts to collect that product-specific safety information in the same setting.

DR. BRADY: I just wanted to clarify, we're just being asked to discuss, but not vote.

DR. DAUM: That's correct.

DR. BRADY: Okay. To me, they are not two mutually exclusive options. Why can't you have them both? Because number 2 is contingent on the actual pandemic occurring, versus 1, which could be occurring without the pandemic.

DR. DAUM: I was waiting for someone to point that out.

DR. BRADY: To me, you don't have to choose one or the other. They both can be done.

DR. GELLIN: Just an observation. One of Robin Robinson’s themes was more and better vaccines sooner. We have been focusing on the better part. But also in Dr. Bresee’s presentation, he told us the reality of the vaccine effectiveness of current products. We have talked a lot about trying to have improvements.

So what worries me a little bit about number 1 is what the public’s expectations might be of the performance of a pandemic vaccine. Knowing what we know about adjuvants, we hope that they are the magic that they have been talked about and will improve the performance, not just the immunogenicity. Given the severity of the kind of pandemic we’re worried about, we would want to have significantly better effectiveness. We would hope for better effectiveness than we’re seeing currently.

I only say that because I don't think it’s really a parallel. Using the current unadjuvanted seasonal vaccine as the basis -- we hope that adjuvanted vaccine is better than that, but we wouldn’t want the people to think that we’re going to settle for something that is of the kind of vaccine effectiveness we have been talking about.

DR. DAUM: Thank you. I think that’s a very important comment.

Ms. Boyce, did you want to say something?

MS. BOYCE: Yes, I do. Then Dr. Innis also has a comment.

I just want to respond to your question. In fact, we are proposing option 1, but we're also agreeing to do option 2, in collaboration with the government. The distinction is that number 1 would be a regulatory requirement and number 2 would be an agreement to work with the agency.

DR. INNIS: Bruce, I hear what you say.

Could we have the slide up?

I think the data that issue from the quadrivalent study, when you consider the clinically consequential disease, classified as moderate to severe -- here are the estimates of efficacy of unadjuvanted vaccine that would be the basis for labeling something, I suppose, in the product information. This is against the influenza A subtypes that occurred in that trial. Those are very respectable estimates of risk reduction for clinically consequential disease.

DR. DAUM: Thank you for that comment.

Before we wind down or take people's last shots -- we're not asked to vote on this question -- I would like to ask the agency whether they are getting the discussion points that they hoped for. I think we have had

a pretty thorough airing of possibilities, but I would like to hear what you think.

DR. GRUBER: While I'm listening to this discussion, I'm reminded of the many, many hours -- the month-long discussion that we had in the Office of Vaccines, where we were debating option 1 versus option 2. It is not an easy, simple answer to that.

I believe we have heard you. We heard the different opinions. Personally, did I get the discussion I wanted? I think I got the discussion that I expected. So I'm fine.

DR. DAUM: I'm quite sure that's not what I asked.

We are going to wind down soon. But, Dr. Cheung, you haven't spoken on this issue. May I call on you, please?

DR. CHEUNG: Personally, I would go for number 2. Number 1 is doable, but I have a little doubt about the neutralization titer. Can we assume that the H5N1 is the same as the seasonal influenza? So it may be a good idea to do both. Obviously number 2 is more difficult, since we don't know when it's going to happen.

DR. DAUM: Thank you very much.

Are there other comments from the committee or the sponsor or any agency issues that have not been raised?

Dr. Piedra.

DR. PIEDRA: Just a pragmatic comment. I think it is very important as to what is labeled when one approves these types of vaccines. I say that because if we look back at the 2009 H1N1 experience, the uptake with seasonal influenza during that time was tremendous. It was very good. It was better than 2008. Yet the uptake with a pandemic vaccine was not as favorable. In part, it was because of a lot of things that were stated out in public, in the different media, with regard to safety issues. If we have things in the labeling that make pandemic H5 vaccine questionable, I think the uptake is going to be seriously in question.

So we have to be, I think, very cognizant of how we label these types of vaccines as they are approved. If we say that we have no efficacy data and just rely simply on safety and immunogenicity, we may not have very good coverage in the public domain. I think that would not be in their best interest.

DR. DAUM: Thank you for your comment.

Dr. James.

DR. JAMES: Just to reply to that, currently we have seasonal influenza vaccines that are approved under the accelerated approval regulation. GSK presented today that their FluLaval is currently in-house for review for

traditional approval. That’s a seasonal influenza vaccine under accelerated approval. I don't know what the uptake of FluLaval is, but it has that same wording that we would use in any accelerated approval.

The other point is that I agree that the H1N1 pandemic vaccines seemed to have poor uptake. But those were approved not under accelerated approval regulations. They were traditionally approved as strain changes. So they did not have accelerated-approval language in their labels. That can’t be pointed to as the reason for the poor uptake.

DR. PIEDRA: My comment is public perception. If we do things that augment the public perception as to its efficacy or safety, we put in question as to its use, its widespread use. I think that’s what happened with the 2009 H1N1 vaccine.

DR. DAUM: And you have to wonder what the public perception would have been if the mortality rate had been close to 50 percent.

Other comments? We’re coming to the bewitching hour of closing. Tomorrow there will be no controversies like this. Dr. Hudgens.

DR. HUDGENS: I would be more supportive of number 1 if it was an adjuvanted seasonal flu vaccine. We have seasonal versus pandemic, quadrivalent versus

monovalent, adjuvanted versus unadjuvanted. QIV-006 is in children, and we're talking about inferring something about adults. So there are four variables, four things that are different that require you to make that inference or extrapolation. Some of those we can't do anything about. But it seems that perhaps it's feasible to entertain the idea of an adjuvanted seasonal flu vaccine, and it seems quite feasible to do it in adults instead of children.

That's my comment on number 1.

On number 2, the terminology "effectiveness" and "efficacy" studies I think is used differently by different people in the room. I understand that most of the discussion regarding number 2 is whether or not we could plan carefully case-control studies like the Canadian studies that were done, perhaps with GSK and CDC and FDA in some collaborative effort. I think that sounds like a great idea, and I'm very supportive of that.

I wonder also -- and this was a question I asked earlier that never was answered -- whether or not it would be feasible during an H5N1 pandemic to do a partial efficacy -- was that the phrase that was used? -- like the 035 study that was done in 2009.

I see you shaking your head. Why would that not be feasible?

DR. DAUM: I don't know who you saw shaking their

head, but we'll ask whoever that was to respond.

DR. INNIS: I was shaking my head, no, it could not be done. The reason is that when you do a clinical trial, to have the trial ethical, there has to be a position of equipoise between the treatments. You don't know that there is going to be a difference. With an H5N1 pandemic, where there would be the expectation of a reasonable risk of death if one could not prophylaxed, there's no question that the unadjuvanted arm and the adjuvanted arm would probably not be equivalent. There would be a treatment difference in favor of the adjuvanted arm. I think IRBs would never approve such a trial.

DR. HUDGENS: So we already know there's benefit. Is that what you're saying?

DR. INNIS: Yes. I think all of the data that we have shown you suggests that -- the dogma here is that more immunogenicity is more protection. We don't know the exact shape of the curve and we don't know where that plateaus at the bottom and at the top. But I think most people who have studied influenza will tell you that more immune response is more protection. And that's what these adjuvanted vaccines do. Remember, the currently licensed vaccine affords a geometric mean titer in healthy adults of 1 to 28. This vaccine augments that 43-fold. So presumably it is a better vaccine.

I know there are a lot of ifs, but we showed you that in the relative efficacy trial that looked at the incremental benefit in the H1N1 pandemic context, there was a 77 percent improvement in risk reduction over the unadjuvanted vaccine. So some similar increment of risk reduction will be seen over what is currently licensed if the adjuvanted vaccine can be deployed.

I also would like to say that what Dr. Piedra said resonates with me a great deal. You are being asked to make a decision. Will you put your imprimatur on the potential effectiveness of Q-Pan based on the data that you have seen today? And if there’s anything in the label that suggests that there are uncertain risks about rare but serious diseases, the public may have questions about what the true risk-benefit is. They will assess that potentially differently from you. You are all professionals. You do this for a living.

DR. DAUM: Thanks for your comment.

I’m going to suggest that we adjourn for the day, but before I do, I would like to say that, irrespective of what this discussion means in terms of the agency deciding how to move from accelerated to traditional approval, should a pandemic occur and this vaccine, which we have suggested today should be approved by the accelerated route, be available and stockpiled and then used, it would

be morally objectionable to me to not attempt to conduct option 2. I look to the company and the government to play nice together and make sure that this gets done. I think we owe it to each other and we owe it to our public to make sure that this is effective should an epidemic occur.

I think that’s really it for today. We’ll see you tomorrow morning at 8:30.

(Whereupon, the meeting was recessed, to reconvene the following day at 8:30 a.m.)