circulating strain, then it can certainly, we'll call it, flatten the curve and buy time in which that vaccine can achieve the first goals that I mentioned and to be used until that well-matched vaccine is available.

DR. SELF: Thirty-three percent is a level of efficacy of the vaccine or 33 percent match to get a certain level of efficacy? What we're seeing here is a weakly immunogenic vaccine, only maybe 40 or 50 percent responding at levels that might be protective at all. So that 33 percent, if it's efficacy, might be very difficult to achieve with this kind of vaccine?

DR. ROBINSON: In different modelings -- studies that have been done by Neil Ferguson, and others, the 33 percent I use is a mean of what they see, and that is on -- is how well-matched it is and also combining then also with the amount of efficacy one might see as preventing death

or very severe disease.

DR. KARRON: Actually, don't go away just yet. I have a follow-up question for this which is related to the use of this vaccine again and some of Dr. Word's questions. So the real intent of this vaccine is to be used for first responders to maintain order, etcetera? There's not -- is there an intent on the part of HHS at this point to use it beyond that level to stockpile beyond that level?

DR. ROBINSON: At the present time with a 90 microgram dose, and you see where we are right now with about enough vaccine for about 16 million persons with clade 1 and clade 2, that is what we'd use it for. As discussions will go this afternoon and in future vaccines development and we have more -- and we can see antigen-sparing that can be safely accomplished, then we'll have to revise because then we would see -- we'd have vaccine stockpiles

that could be for many more people. But prioritizations right now are based on the 90 microgram dose.

DR. KARRON: For this vaccine right now?

DR. ROBINSON: That's correct.

DR. KARRON: I have two very specific questions for John Treanor, just clarification questions. One is actually related to slide 17, and I just wanted to clarify there were a number of subjects receiving one, two or three doses?

DR. TREANOR: Right.

DR. KARRON: And I just wanted to clarify are those -- those are subsets, so --

DR. TREANOR: They're all subsets of -- there's no one who received two doses who did not receive one dose if that's what you mean.

DR. KARRON: Right. So they're all subsets of the 363? Yes. Okay. The --

yes. The other question that I had was I know we'll have discussions about boostablility this afternoon, but in this particular study or as a follow on to this study, we saw the antibody titers at six months post vaccination. Were any of those subjects boosted and do you have any information about that?

DR. TREANOR: I think that data hasn't been completely finalized yet. We will have data on the response of individuals in the 063 study who received a third dose, and that will, at some point in the near future, include both safety and immunogenicity data for those subjects.

DR. JACKSON: While John's up there, John, was there any relationship between response to the first dose and response to the second?

DR. TREANOR: I don't have that analysis.

DR. KARRON: Dr. Modlin?

DR. MODLIN: Sorry to be persistent, but I wanted to go back to the last question I had, and it's I don't quite understand the rationale for labeling this for clade 1 use, if indeed, as proposed, this vaccine would be used in the event that we had a clade 2 outbreak. Would this require -- if we had a clade 2 outbreak, would it indeed require use under IND if clade 2 is not included in the label? This is maybe -- it's a sticky regulatory issue, I understand, but potentially an important one.

MS. BACHMAN: I'll answer you, John. I think we're -- the indication is not final yet. I mean this is the proposed indication from the company. We have to keep in mind sort of what situation will we be in. I mean if we labeled this vaccine as clade 1, I mean that does not prohibit -- I mean it's -- it would sort of be like, and I think somebody mentioned this earlier, that we had

the seasonal vaccine and there was a mismatch. We wouldn't say stop using that vaccine. We would continue to use the vaccine that we had decided upon the strains and perhaps there would be some protection, but, again, we would not stop using that vaccine.

So in this situation, if we had that -- even if the vaccine, the label was clade 1 and this is all we had, we did not have a vaccine against Indonesia, we -- it's a policy decision whether we would continue to use that. But keep in mind that we are, or at least there are data being generated with Indonesia, and so, again, I think we really have to keep in mind this is in the interim. I mean we're not just freezing in time. As we evaluate this vaccine to sort of get us through this period as other vaccines are being developed and other vaccines are being developed rapidly and we need to look at those clinical data and

we're moving into other generations of vaccines of all types for pandemic, so we have to keep a frame of reference here.

DR. KARRON: Dr. Webster's going to ask the last question and then we'll move on. We'll have time for discussion after.

DR. WEBSTER: No. I'm going to make a comment on clade 1-clade 2 cross-protection. The information is just not available at this time in humans, but the animal studies already indicate that vaccination with a clade 1 virus in challenge for the clade 2 gives considerable protection. So it's -- I think it might come down to the labeling issue. There is more and more information coming on cross-reactivity between these clades.

DR. KARRON: Thank you. I think we'll move on now to hear from Dr. Davis on Post Marketing Safety Monitoring During an Influenza Pandemic. It's Dr. Shay on effectiveness first.

DR. SHAY: Thank you and good morning. I've been asked to speak briefly about CDC's plans to monitor the effectiveness of pandemic influenza vaccines. Of course, limited immunogenicity and safety data will be available prior to distribution of any pandemic vaccine and safety monitoring will be essential. Post licensure safety studies can begin in a pre-pandemic use of each product and continue throughout the whole vaccine program. And if desired, post licensure immunogenicity data could also be collected in a pre-pandemic setting.

Data concerning clinical effectiveness of pandemic vaccines will be essential, of course, and immunogenicity and protection from illness are imperfectly correlated. Different populations may receive vaccine in pre and post licensure situations as well. And we, of course, always need to consider issues of vaccine

match and perhaps the need to change the strain of a pandemic vaccine during the course of a pandemic. But obviously, studies of clinical effectiveness must await the onset of a pandemic and illness in populations who are eligible to receive stockpiled or pandemic vaccine.

So as we talk about CDC's vaccine effectiveness plans, we'll define effectiveness as protection against influenza illness when vaccine is administered in the context of an immunization program and that is outside a randomized clinical trial. Effectiveness may vary by age, by medical history and immunocompetence of the vaccine recipient. And effectiveness, we can expect, will vary with the outcome studied as well such that it'll be lower for non-specific illnesses that may be caused by pathogens other than a pandemic virus and that it may vary with the severity of the outcome being studied

whether that's illness, hospitalization, more severe illness such as need for mechanical ventilation or death. We'll also need to plan to assess effectiveness after one and two doses of vaccine.

Our existing plans for pandemic vaccine effectiveness assessment is really built on our existing influenza vaccine effectiveness projects. Two of these projects build on existing surveillance systems for influenza and those are the Emerging Infections Program or the EIPs and the New Vaccine Surveillance Network or NVSN. The third project is one with the Marshfield Clinic Research Foundation which was funded to provide rapid, within season estimates of vaccine effectiveness against a laboratory-confirmed outcome. And all our existing studies do use laboratory-confirmed influenza illness as the outcome, although the specific outcome does vary with the study.

So this is a map showing our population-based influenza surveillance at present. There are 12 Emerging Infections Program sites scattered throughout the country in those orange areas that mark the counties in which influenza surveillance is done. Currently, in the EIPs, children less than 18 years hospitalized with laboratory-confirmed influenza infection are the surveillance group, and adult surveillance began in January of '06 as a pilot in several of the sites.

The New Vaccine Surveillance Network is in three counties, Hamilton County, Ohio at the University of Cincinnati, Davidson County in Tennessee with Vanderbilt University, and Monroe County in Rochester, New York in the University of Rochester. And those latter two counties overlap with EIP surveillance.

In these sites, children less than 5 years with inpatient or outpatient

laboratory-confirmed influenza infection are the cases that are sought. And outpatient surveillance in children age 6 to 12 years started this season.

So to go over these studies in a bit more detail, the EIP study is a case control design. It was piloted last season and will continue this season in '06-'07. The setting is hospitals, last season, in six of the EIP sites and this year in nine of the EIP sites.

The cases are children aged 6 to 23 months old in '05-'06 and 6 to 59 months this season to reflect the ACIP recommended age groups for receipt of vaccine.

Cases are children hospitalized with laboratory-confirmed influenza as by test ordered by clinicians, and the most common test ordered are DFA, rapid antigen detection, and culture in that order. Controls are age and zip-code matched children not hospitalized with influenza.

Vaccination data are sought from healthcare provider report and by parental report via telephone interview.

The sources of other data include medical chart review by the provider and, again, parental review. And some of the other data collected are age, gender, race, insurance status, high-risk medical conditions, socioeconomic status, smoking in the household, those sorts of variables.

The New Vaccine Surveillance Network studies now also include case control studies. Therefore, studies were done in the '03-'04 season and continue up into the present season.

The setting for these studies are hospitals, emergency departments, and outpatient clinics, again, in those three counties. The children are aged 6 through 59 months. The cases are children brought to medical attention with fever or acute respiratory who test positive when enrolled

in a -- by study nurses for influenza, by culture, or RT-PCR.

And controls are children, in the current studies, with fever or ARI, again, brought to medical attention who test negative for influenza by culture and RT-PCR. Vaccination data are obtained again from healthcare providers.

Other sources of data are sought through medical chart review by abstractors and again by parental interview. And other data collected in this set of studies are age, gender, race, insurance status, again, high-risk medical conditions, socioeconomic status and other factors that are known to be risk factors for hospitalization with viral respiratory pathogens in children.

And finally, the Marshfield Clinic studies include cohorting case control designs. These studies were started in the '04-'05 season and continue to the present. The setting here is a clinic

population in North Central Wisconsin where a very large majority of the population receives their care through the Marshfield Clinic and their affiliated clinics.

The age group that is studied is all individuals for whom ACIP currently recommends annual vaccination. Cases in this set of studies are patients seeking care for acute respiratory illness who are influenza positive by culture or RT-PCR. And again, the cohort is a set of adults and children for whom ACIP has recommended annual vaccination and a cohort analysis is done.

In addition, there are age-matched controls without ARI symptoms who are in the same healthcare system. And again, as is done in NVSN studies, also a set of test-negative ARI controls.

Vaccination data in the Marshfield studies, what makes them rather unique, is obtained from a regional

electronic vaccine registry that includes all vaccinations essentially given in their service area, so even if you get your vaccine at Kroger. Other sources of data include electronic medical record and interview of the patients. And again, Marshfield has a totally electronic medical record, so data such as age, gender, race, high-risk conditions, and propensity to seek healthcare as assessed by previous healthcare visits is accessible, essentially, immediately.

To use any of our existing systems to look at vaccine effectiveness, we have to think a little bit about pandemic vaccine prioritization and how stockpiled and other vaccines will be used. Everyone will be susceptible, of course, and U.S.-based production capacity is not currently sufficient, as we all know, to provide vaccine rapidly for the entire population. It is assumed that the earliest doses of

vaccine will be available approximately 20 weeks after isolation and characterization of a pandemic virus.

So many of you, I am sure, are familiar with the ACIP and NVAC priority groups for pandemic vaccine. This was the joint work of the two HHS committees, and the process entailed consideration of estimates of vaccine supply and effectiveness, the effects of pandemic by age and risk groups, and the potential effects in critical infrastructure and healthcare. And the recommendations from ACIP and NVAC were included in the 2005 HHS pandemic plan as guidance for state and local planning and to promote further discussion.

And so sort of the top two ACIP priority groups were 1-A, vaccine and antiviral manufacturers and medical workers who are involved in direct patient care contact and support services, so about 9

million people. And the second group were those the committee felt would be at highest risk for pandemic-associated outcomes, included persons age 65 or greater with one or more influenza high-risk conditions or 18 million people, approximately; persons aged 6 months through 64 year with two or more high-risk conditions, another 7 million; and those 6 months and older with a history of hospitalization for pneumonia or influenza in the past year, so another 700,000 people.

Again, there has been considerable discussion. After the ACIP recs, an interagency pandemic vaccine prioritization workgroup was formed and include participants from multiple federal agencies. They considered the ACIP and NVAC recommendations and considered the National Infrastructure Advisory Council recommendations on critical infrastructure sectors that would be most important, and there have been public engagement meetings

and the stakeholders meeting.

And there's a summary of those meetings. At each of the three meetings, the most highly rated goals were the same, and that was maintaining critical societal functions, protecting those who would help others during a pandemic, including healthcare workers, and a priority placed on protecting children, especially against pediatric mortality.

Most other goals were considered modestly important and those included protecting those most likely to get sick or die during a pandemic and although the ranks and rank order did vary between these meetings.

This group has developed draft prioritization guidance, is going to hold additional meetings, solicit written comments. ACIP, for example, was updated very recently by Ben Schwartz of NVPO on this work. And this working group will also

consider pre-pandemic vaccine prioritization and will modify guidance -- how to modify guidance at the time of a pandemic. Final guidance is expected by May and, of course, all these considerations influence how we are thinking about needing to be prepared to monitor effectiveness of stockpiled and other pandemic vaccines.

So with those considerations in mind, here are present sort of plans. We will study laboratory-confirmed outcomes. Hospitalizations, for example, are well-captured in several of our systems and our severe -- additional more severe outcomes may also be studied such as all-cause mortality depending upon the nature of the pandemic. Obviously, it will be much easier to study such an outcome in a severe 1918-style pandemic than in a '68-'69 pandemic.

And of course, observational studies outside the context of randomized trials must collect data on possible

confounding factors between receipt of vaccine and outcomes. Selection bias, for example, is likely but we can't assume the direction. In older individuals, if those with more severe out -- more severe underlying diseases are prioritized for receipt of vaccine, they are likely to be more ill than the underlying population of people that age.

On the other hand, if the vaccine goes to very narrow groups of younger people such as firefighters, they may be more likely to be healthier than the underlying population in that age group.

And of course, we will need to link existing individual health data to vaccination and outcome data to control for these possible confounders. And our plans will continue to evolve as vaccine priorities develop. For example, again, our existing systems cover children well but specifically in the context of this vaccine

that's being spoken about this morning, community based studies may not be as very efficient if initial vaccine is prioritized to a few critical infrastructure sectors and we'll have to take other study designs to get at those individual, small populations.

Also, we need to think about vaccine distribution and tracking methods. State and regional registries may be used to identify vaccinated individuals if all available pandemic vaccine comes through government sources. But again, there will be a need to link pandemic vaccine receipt back to the medical home, if you will, such that medical and demographic data are able to be collected and used in analysis of effectiveness.

We also have plans to expand our existing systems. For example, in the future, hopefully, we could study effectiveness among adults, hospitalized adults in the EIP system. We would also be

interested in expanding the rapid method used by the Marshfield Clinic to other sites that have electronic medical records. There's also the potential for new systems. For instance, consideration of using our sentinel provider system and some of the point of care diagnostic tests that Robin Robinson referred to that are being developed under HHS contract.

And finally, CDC is eager to work with our governmental and other partners to make sure that we're able to provide effectiveness data that meets the needs of the nation.

Thank you. And I'd just like to acknowledge those people who contributed to this presentation.

DR. KARRON: Next we'll hear from Dr. Caubel about the Sanofi Plan for Pharmacovigilance.

DR. CAUBEL: Good morning. My name is Patrick Caubel. I am Head of

Pharmacovigilance for Sanofi Pasteur in North America. Planning for the prospect of pandemic influenza is one of the most effective steps to mitigate the impact of such an event. Preparing for the next influenza pandemic requires support and collaboration from multiple partners at the state, national and international levels.

Vaccination remains a critical defense against a pandemic influenza. Vaccine safety monitoring is critical and should be part of a comprehensive plan, public health surveillance program in which we are committed to take part.

Pharmacovigilance plan objective -- the objective of the pharmocovigilance plan should be to detect, to evaluate and to minimize the potential risk due to the pandemic influenza vaccine. It should contribute to the benefit risk evaluation in a pandemic situation. There should be an agreement on several objectives. Number

one, the objective for the post marketing safety surveillance; number two, a collaborative plan with the key stakeholders; and number three, we have to establish a system which is going to function in a pandemic situation.

Pharmacovigilance planning will be critical in a pandemic situation. Pharmacovigilance activities have to be designed considering the following constraints: Number one, there will be limited clinical data available prior to the onset of a mass vaccination. Number two, a high volume of safety data, mostly spontaneous reports, is anticipated during a very short timeframe.

Number three, an increased public anxiety with adverse events reported is expected regardless of the causality. Any adverse event reported of any size is going to increase -- most likely are going to increase the level of public anxiety.

Number four, limited qualified personnel will be available in the industry and regulatory agencies. And finally, the pharmacovigilance stamps are very likely to be disrupted. In addition, there is a need for an ongoing safety signal detection and evaluation in order to enable appropriate decision with respect to the vaccination campaign.

And finally, the feasibility and effectiveness of appropriate actions and measures need to be tested prior to the onset of a pandemic.

I'm going to try to distinguish between what may happen during the pre-pandemic period and during the pandemic period itself. So during the pre-pandemic period, the usual routine pharmacovigilance practices will apply. Start out spontaneous report will be collected routinely. Aggregate reports will be produced at different time intervals. Signal detection

and analysis will be conducted at also regular intervals. Safety surveillance studies could be initiated and one can think of possible cohort study in the first responders who are going to be vaccinated prior to the onset of a pandemic.

Passive collection of vaccine federal reports are going to take place as it is usual for any vaccines. The objective of this plan in the pre-pandemic period is to develop a better understanding of a vaccine safety profile that could impact the pandemic safety monitoring.

In a pandemic situation, we propose that some changes to the usual pharmacovigilance practices are considered. Number one, we would like to proceed a more focused spontaneous reporting on adverse events of high safety importance. We would like also to consider simplified aggregate reports focusing on the issue of real public health interests.

Number three, we feel that the real time signal detection analysis is necessary to allow quick decision making on the vaccination campaign.

Number four, we have the need for a safety surveillance study in earlier recipients after the pandemic is declared. And number five, the passive collection of vaccine federal reports will continue as usual.

The objective of this proposed revised pharmacovigilance practice is not to diminish the level of safety surveillance but more to allocate the available on tasks critical for understanding the evolving benefit-risk profile in the pandemic situation. We think that we need to focus on the information on the analyses which are going to provide the most relevant information to -- in order for the authority to make the appropriate decisions.

I would like now to examine the

critical steps that could be impacted -- critical pharmacovigilance steps that could be impacted in a pandemic situation. Number one, the spontaneous reporting -- data collection -- well, spontaneous reporting will remain the basis for safety evaluation. We think that one, common, simplified and targeted collection form could be used by all parties when the vaccination process begins. It should help to focus on the collection of the most important adverse events and for safety monitoring of pandemic flu vaccine.

Healthcare professionals and patients were very likely to be the primary source of information and should also be encouraged to report primarily serious adverse events, life threatening adverse events, adverse events of special interest. And I will come back to that later --

Adverse events of special interest -- all parties, in fact, must

consider a list of adverse events of special interest for which a common case definition will be used in order to ensure harmonized safety analysis of cases. Europe has already proposed a list of adverse events of special interest for pandemic flu vaccines survey and we propose that the key stakeholders in the U.S. who are on a similar list of adverse events have special interest.

Focusing our safety analysis on these terms without neglecting, and I want to be sure it's quite understood, we weren't neglecting the rest of it, that declaration could lead to a quicker identification of a potential safety signal.

The safety database is the repository in which key safety analyses are going to be conducted during the pandemic period. It is important that all stakeholders seed the database with all safety information available. The rapid and

open communication and information sharing between Sanofi Pasteur, other vaccine manufacturers and authority, public health and public health services is absolutely essential, and electrical communication also should be established prior to the pandemic period. One single safety database dedicated to flu pandemic vaccines could be used and shared by all parties and, for example, a subset of a VAERS database could meet these goals.

Aggregate report or period reporting -- Periodic Safety Update Reports are prepared at define time intervals. However, during the pandemic period, due to the limited resource, preparation and submission of PSUR may not be feasible. So we think that several options might be considered. The first one could be to have some what we call simplified PSUR focusing on serious adverse, even death, life-threatening events and adverse events of

special interest.

Another option could be to have a PSUR prepared on ad-hoc bases upon request from authority if any suspicion of potential signal or potential issue emerges. Of course, an aggregated PSUR will be prepared and submitted with the pandemic is declared finished.

Signal detection is a critical step for identification of safety issues with vaccine and with any pharmaceutical product. The crude inspection of single indicators and line listing is not any more an adequate method to detect a safety signal. We need to consider quantitative and automated data mining methods, for example, using different statistical scores like proportional reporting rates, Bayesian methods to enhance the efficacy of signal detection.

The modification of the standard method might be required, like some specific

stratification by sub-population age group. We need also to identify the appropriate comparator in the pandemic situation. In fact, this data mining may detect an increase in the incidence of the adverse events of special interest and also help in the detection of unexpected adverse events. The signal detection tools and practices should be tested with seasonal vaccine prior to the onset of a flu pandemic.

Monitoring for vaccine effectiveness -- and we just spent some time reviewing this issue -- well, as you know, there is no vaccine which is 100 percent effective, and this applies in particular to the vaccine we are reviewing today. Vaccine failure evaluation done through pharmacovigilance monitoring should not be used to assess vaccine effectiveness, and if you want, I can come back to that later, but the case we are collecting during the pharmacovigilance process are uncontrolled

by nature and not eligible for effectiveness assessment.

Safety surveillance studies are powerful tools to assess the safety profile of a newly licensed vaccine, and this applies as well to the flu pandemic vaccine. The safety profile would remain unknown in numerous populations prior to the vaccination campaign due to the lack of clinical data in sub-populations. So some consideration should be given to initiating cohort study, either pre or prior to the pandemic, for example, in first responders and critical works who, or after the pandemic is declared, like, for example, in the earlier recipients of a vaccine.

Case control study using large population-based databases like Vaccine Safety Datalink may be useful for the analysis of rare adverse events.

These studies, given the complexity, and in particular in the

pandemic situation, should be coordinated by national and international public health agencies.

So in summary, streamlining and prioritizing is essential for early detection and communication of potential risk, and consequently for a good and rational decision making. The pharmacovigilance plan and information system must be tested and harmonized during the forthcoming and subsequent season in order to be sure that it will be fully effective during the pandemic.

The proposed pharmacovigilance actions are part of an evolving plan to be refined with key stakeholders together with a better definition of roles and responsibilities. Of course, you know, Sanofi Pasteur is coming to global pandemic preparedness and last point -- conclusion is safety is, for our vaccine, is of paramount importance for Sanofi Pasteur, and Sanofi

Pasteur is prepared to work with the Government on efficient methods of collecting safety and effectiveness data. Thank you.

DR. KARRON: Thank you, Dr. Caubel. Dr. Ball?

DR. BALL: Good morning. My name's Bob Ball. I'm Chief of the Vaccine Safety Branch in CBER, and I'm going to be talking this morning about two topics, the first is pandemic influenza vaccine safety and effectiveness monitoring. I'll be including some information provided on CDC's plans for vaccine safety monitoring systems by Dr. John Iskander of the CDC Immunization Safety Office. And then I'll be providing some comments on Sanofi Pasteur's H5N1 vaccine pharmacovigilance plan.

So first, some general considerations for why it's important to do post-marketing safety monitoring of pandemic flu vaccines. There is limited safety and

effectiveness data available for these vaccines prior to use. Robust safety and effectiveness monitoring is essential for, really, three reasons. Morbidity due to adverse events may be severe, and the best historical example of that that's relevant here is probably Guillain Barre Syndrome that occurred after the 1976-77 swine influenza pandemic vaccine use. It's also important to alleviate unwarranted fears to strengthen competence among the public in the safety and effectiveness of the vaccine. And finally, this type of data will facilitate benefit-risk analysis.

In recognizing this, Homeland Security Pandemic Influenza Plan has tasked the FDA with, among other things, tracking adverse events following vaccine administration and coordinating the definition of protocols for conducting vaccine effectiveness studies during a pandemic. We've heard already a little bi

this morning about some of the factors that will affect vaccine safety and effectiveness monitoring. Those includes the stage of the pandemic that the vaccine is used, the population receiving the vaccine, and strategy for vaccine distribution. I only want to point out that because of the variety of possibilities, it's important that a robust and flexible system be in place for vaccine safety and effectiveness monitoring.

And I'll shift a little bit and talk about key systems that are currently available to study vaccine safety. First, there is the Vaccine Adverse Event Reporting System, or VAERS, which is the early warning system of vaccine safety surveillance. It's a national passive surveillance system that's jointly operated by CDC and FDA. It's been in place since 1990 and accepts reports from physicians, other healthcare providers , and the public. It's a

hypothesis-generating system that seeks signals of potential concern.

Advantages of VAERS are that it is national in scope, covers diverse populations, and is able to detect rare events in a cost-effective manner. Rapid detection of possible signals is possible through VAERS, and these generate hypotheses that can be tested in other systems. It's also possible to assess lot-specific vaccine safety.

Disadvantages of VAERS include the presence of reporting biases. It's known that if there's under reporting, those serious events are more likely to be reported than non-serious events. And there's also over reporting since many reports that are not causally related to vaccination are also reported to VAERS. VAERS does not provide information on the number of persons vaccinated or the background incidents of conditions in the

general population, so this information has to be obtained elsewhere.

The vaccine safety data link at the CDC was developed to account for some of these limitations of the VAERS system. There are eight geographically diverse health maintenance organizations that participate in a large linked database which tracks vaccination, outpatient, emergency department, hospital, and laboratory data to measure health outcomes, contains demographic variables which can be confounders and covers about three percent of the U.S. population. The VSD can be used to test the hypotheses that are generated by VAERS or other sources.

Advantages of analyses in the Vaccine Safety Datalink include that all medical encounters are available at most of the sites. It allows calculation of background rates of adverse events that can be compared to reporting rates in VAERS.

Medical chart review for diagnostic validation is possible, and it's rapidly available for urgent studies.

Some of the limitations of VSD analyses include that the sample size, although very large, still may not be adequate very rare events such as Guillain Bare Syndrome with an incidence of about 1 to 20 per 100,000 per year is background. Vaccines administered outside of the HMO setting is not captured by the VSD database, and there is limited demographic and socioeconomic diversity in the eight HMO practices. The unvaccinated population may be small and so, therefore, may require special methods for analyzing outcomes.

The CDC also has other resources available for study of vaccine safety. The CDC collaborates with the Brighton collaboration which developed standardized case definitions of adverse events following immunization for use in clinical trials or

epidemiological. CDC also sponsors the Clinical Immunization Safety Assessment Centers, or CISA, which developed standardized patient evaluations for adverse events and can provide clinical guidelines for providers in managing adverse events after vaccination.

Additional data available from the CDC comes from the biologic surveillance system which provides vaccine dose distribution for a calculation of reporting rates of adverse events, though it's important to note that this is not doses administered, simply doses distributed.

There are also a number of surveys from which important information can be gathered including the Nationally Representative Coverage Surveys, National Health Interview Survey, National Immunization Survey, and the Behavioral Risk Factor Surveillance System. CDC also has extensive relationships with state and local

health departments and immunization registries. Hospital discharge and mortality data sets are also available which can be used to calculate background rate of adverse events.

In preparation for pandemic, the FDA and CDC have undertaken some additional activities for vaccine safety. These include pilot projects to assess the use during a pandemic of the VAERS system beginning with the 2006-7 influenza season reports. Also, in collaboration with Harvard, there's a planned expansion of the Vaccine Safety Datalink to another site to expand the number of people under study and evaluation of other large automated databases of encounter and/or claims data for similar use.

The FDA has also begun a pilot project with the Center for Medicare and Medicaid Services to obtain rapid access to data on influenza vaccine and treatment

claims since Medicare beneficiaries are a large group that receives annual flu vaccine. FDA has also begun discussions with DoD and the Veterans Administration on their plans for a pandemic influenza vaccine safety and effectiveness monitoring.

So in expanding the existing systems, a number of principles are important to keep in mind. Complementarity, coordination and minimized overlap between government agencies and vaccine manufacturers to ensure that each is contributing valuable information to safety and effectiveness monitoring is important.

To that end, the FDA has initiated pharmacovigilance planning, and since 2005, has requested that vaccine manufacturers submit a pharmacovigilance plan with their Biologics License Application. These pharmacovigilance plans should follow FDA and International Conference on Harmonization E2E guidelines

on pharmacovigilance planning. And in addition to reporting of adverse events to VAERS as required by regulation, it's often important to have enhanced safety surveillance and/or observational studies as part of these plans.

And it's highly recommended that sponsors work closely with the FDA and CDC to develop and conduct studies to monitory safety after licensure.

So you heard just before me the presentation of Sanofi's pharmacovigilance plan. I'm just going to make two general comments about two aspects of the plan. First, Sanofi has proposed changes to adverse reporting during a pandemic that are not consistent with current regulations include less frequent or simplified submission of periodic update and/or other reports and use of simplified reporting forms.

The FDA has not yet made any

decisions about whether or not changes to adverse event reporting will be needed and what they might be during a pandemic.

Sanofi also does not propose to conduct additional safety or effectiveness studies of the H5N1 vaccine.

As we go forward, there are a number of issues that require clarification for safety monitoring for your consideration. Should specific adverse event reporting requirements be increased or decreased? Do we need to monitor for particular adverse events of interest, and if so, what are they? Who, FDA, CDC, Sanofi, other groups, should be responsible for what aspects of safety monitoring of the H5N1 vaccine? And how might these above considerations vary according to pandemic stage?

Similarly, there are a number of issues requiring clarification for effectiveness monitoring. What outcomes

should be assessed to evaluate effectiveness, that is how should influenza be defined? We heard from David Shay talking about laboratory-confirmed influenza, but it might also be necessary to evaluate off-course mortality in large claims databases. What study design should be used to evaluate effectiveness to account for some of the issues that David mentioned about biases in certain study settings? And then who should be responsible for what aspects of effectiveness monitoring of the H5N1 vaccine, and how might this vary according to pandemic stage?

So finally, a robust and flexible safety and effectiveness monitoring system is needed to address the range of possibilities during an influenza pandemic. Epidemiological studies will likely be important, and close coordination between Government agencies an Sanofi Pasteur would be beneficial. And it's desirable for

Sanofi to commit to working with the FDA and CDC to fill the gaps in collection analyses of safety and effectiveness data if the H5N1 vaccine is used.

And I'd just like to acknowledge those who helped with this presentation. Thank you.

DR. KARRON: Thank you. Questions or comments for any of the previous three speakers? Dr. Wharton?

DR. WHARTON: I think in thinking about how to monitor safety and effectiveness, it's really important to keep in mind that we don't know how the vaccine is going to be distributed. And this was implied by a number of speakers, but just to make it clear, if we are using a vaccine distribution system similar to what we use for seasonal influenza where vaccine is distributed through multiple providers, many of them healthcare providers that are involved in our existing networks, then our

existing infrastructure may be very helpful in looking at both effectiveness and safety, because we're likely to capture those populations that are being immunized.

But for some of the possibilities for how a severe influenza pandemic might play out, we could be dealing with a quite different distribution system. So if, for example, we were targeting first responders, those are unlikely to be captured by the VSD, and these critical infrastructure workers are not the usual target group. So just to make that really clear as we're thinking about these things, that we may need quite different systems than we currently have to answer some of the questions that will be important to answer.

DR. KARRON: Dr. Hetherington?

DR. HETHERINGTON: I wonder if we have any clarity on how first responders are identified, and you obviously will have a limited number of doses of vaccine

available, so how will people be designated as receiving? If, in fact, they are heavily concentrated within the governmental agencies, wouldn't there already be a database available that would be able to be mined for safety follow-up in a sense?

In follow-up to previous question, in fact, there may be a structure that's available if we know who the first responders are and we know where the links to their healthcare reside, whether they're in a governmental database or some specific HMO. So that -- I wonder if that's been given any thought by the FDA or anybody else?

DR. GELLIN: Let me comment on that. And as David Shay presented in his description of the ongoing process, there is currently a revisiting of the prioritization for vaccine in a pandemic. And the biggest difference is really the incorporation of the input by the National Infrastructure

Advisory Council, I think it's called, which is a DHS Homeland Security Advisory Council, to get a better sense of who in the critical infrastructure is critical. But you raise an important point because, as Melinda highlighted, it's likely particularly early on to be distributed differently than seasonal vaccine.

So I think that is important -- so I don't have a clear answer for you other than I think you highlighted that recognizing that there are different systems of care for these people that we should look at whatever existing databases might be able to capture that care, whether they're in the Defense Department, whether they are in Occupational Health or whatever. But I think that that's an important consideration.

DR. KARRON: Dr. Farley?

DR. FARLEY: Given all the complexities of not knowing in advance,

really, how this will be introduced -- I mean having some general concepts -- and it will be somewhat unprecedented in terms of if we launch a major campaign against pandemic flu or at least it's been many -- it's been a generation or so since we've had to do anything like this, and we will potentially have larger stockpiles, have actual access to vaccines in a more timely fashion -- I mean how practical would it be to force a registry process into this so that each and every individual who receives a pandemic flu vaccine go into a national registry regardless of age and whether it be building upon old systems or having a dedicated system to this event? I don't know who might be able to answer that but maybe Bruce.

DR. GELLIN: Let me start and others may add to that, but among the investments that are being made of this in a pandemic budget is looking at registries.

And I think the question you raise is whether or not existing registries or some alternates. Because I think that here is the opportunity to do many things, not only to monitor both safety and potentially effectiveness, but it also is the complexity of this is a two-dose schedule. You want to ensure that those who get the first dose get the second dose as well.

So I think that -- I don't know if anybody wants to comment on that specifically other than there is a -- that's recognized as one way that there might be a system either building on existing systems or creation of a slightly different system to be able to accomplish those three goals.

DR. WHARTON: Yes. Just to extend what Bruce said, at least what the immunization program grantees tell us is that they are planning -- the majority of them are planning on using their existing immunization registries as part of their

activities.

Now at this point, state programs are going asked to make pandemic plans and I think this is on the assumption that there will be a state health department directed public health activity that will be I charge of the initial states of vaccination. So it certainly is possible but the existing immunization registries can help with this. I do have to say that there are concerns about the capacity of those registries as they currently exist to actually fulfil this function, but at least the majority of state programs have told us that is what they plan to do.

DR. KARRON: Dr. Couch?

DR. COUCH: Just thinking back a little bit about 1976. When you start vaccinating everybody, you're going to need a frame of reference for a likelihood of events that will be occurring. Because you see, Guillain Barre was unanticipated. The

deaths that occurred in Pittsburgh, you stopped that, you know, and that campaign was a little bit different. But you have to say that's not -- that's expected, you see, and be able to respond to that without a control group, because everybody's going to be in line to get their vaccine. And one of the options for that might be rapid response teams to something like the VAERS reports that can trace these, because they'll end up in the headlines of the local newspaper, and the local newspaper will cause all the talk programs and everybody else to start questioning safety unless you're prepared to respond.

DR. KARRON: Dr. Jackson?

DR. JACKSON: I just had a question for Dr. Wharton. When you say existing registries, what do you mean?

DR. WHARTON: Well, I'm not sure what the grantees meant. What they have reported to us is that they planned on using

their immunization registries. Some of these are state. Some of them are local. But these All right. considered to be public health programs that are largely run by the public health infrastructure, so I assume these would be the governmental registries as opposed to private sector registries.

DR. JACKSON: So primarily childhood vaccination registries?

DR. WHARTON: Yes. And I think that's one of the capacity issues is that the registries were originally developed for childhood immunization although some states have now extended them to adults and there's no a priori reason that other states couldn't do that, but that is one of those capacity of infrastructure issues that raises some issues about whether or not these registries have the capacity to do that.

DR. KARRON: I think we'll have more discussion of this topic after the

break. We have a fair amount of time budgeted for post open hearing discussion. So we'll take a break now and reconvene at 11:00 o'clock. Thank you.

(Whereupon, off the record at 10:45 a.m. and back on the record at 11:12 a.m.)

MS. WALSH: I think we're ready to begin. I'd like to ask everyone to please take their seats. Next on the agenda is the open public hearing. As part of the FDA Advisory Committee meeting procedure, we are required to hold an open public hearing for those members of the present who are not on the agenda and would like to make a statement concerning matters pending before the committee. I've not received any request at this time. Is there anyone in the room who would like to address the committee?

(No response.)

MS. WALSH: Dr. Karron, I see no

response and I will turn the meeting back over to you.

DR. KARRON: Thank you, Christine. At this time, we will have the FDA presentation of questions by Dr. James.

DR. JAMES: Okay. I've already given you the proposed indication. I will repeat it once again. Sanofi's proposed indication is that H5N1 Influenza Virus Vaccine A/Vietnam/1203/2004 (Clade 1) 90 micrograms per milliliter is an influenza viral vaccine indicated for active immunization against influenza disease caused by H5N1 A/Vietnam/1203/2004 (Clade 1) influenza virus and primary vaccination of healthy adults 18 through 64 years of age.

The first question to the committee is are the data sufficient to support the effectiveness of this product for use during a pandemic or in situations of potential high risk exposure?

Second question. Are the data

sufficient to support the safety of this product for use during a pandemic or in situations of potential high risk exposure?

And the last question is please comment on studies to collect additional information about the effectiveness and safety following this vaccine's use.

DR. KARRON: Thank you, Dr. James. I'd like to open this up for discussion, but I actually will lead off with perhaps a question for you, Dr. James, if you don't mind. And that is I know that there's been a lot of discussion during these proceedings this morning about how and when and in whom this vaccine might be used. Am I to understand from the way this question is written that the vaccine would be used during a pandemic but not pre-pandemic, for example, in first responders? Is that -- am I understanding that correctly?

DR. JAMES: You are understanding

that correctly. Sanofi did not phrase their indication, did not propose their indication that way, but we're specifically, the FDA is specifically asking you to consider the data that we've presented for use during a pandemic or in situations that may occur prior to a pandemic but that are potentially high risk exposure situations.

DR. KARRON: Ms. Province, did you want that clarified that last statement? Is that --

MS. PROVINCE: Yes, please. I'm sorry, it just seemed that you answered it one way and then answered it another way or maybe I misunderstood you.

DR. KARRON: I think that what maybe you were asking for is a clarification of what high risk exposure constitutes. Could you give an example of that.

MS. PROVINCE: You phrased that better than I did. Yes, what would constitute the high risk exposure? Would

that be the first responders prior to pandemic?

DR. JAMES: First responders, military who may be deployed to Indonesia for whatever reason. Yes, high risk basically would be first responders and the like.

DR. KARRON: Dr. Self?

DR. SELF: Thank you. I work better when things are really concrete, so I'm trying to imagine, you know, what might actually happen. There are some transmission chains that happened in Indonesia or somewhere in Southeast Asia, a couple of cases start showing up around our airports, and then this -- those sorts of events would trigger the use of this vaccine among first responders followed by the 600 million dose reference 6 months later of some other vaccine or of this vaccine? Is that a scenario that we're talking about?

DR. JAMES: I actually would ask

-- well, it looks like Norman wants to respond first.

DR. BAYLOR: I'll respond. I mean first off, I mean how this vaccine will be used other than during a pandemic, I mean these are policy decisions. But you may have examples where you start getting spread to human transmission from human-to-human, and a decision may be made at that time that, yes, we should start, you know, deploying this vaccine. Or you may have individuals going into a region where there is a human-to-human spread or even avian, there's a high level of avian influenza in the area. So these are decisions that will -- you know, they're policy decisions but thee are opportunities where this vaccine might be deployed.

DR. SELF: And then what's the relationship of this vaccine to the vaccine referred here, the 600 million --

DR. BAYLOR: Whose slides are you

looking at?

DR. SELF: Six hundred million doses -- well, I ask because, you know, part of our charge is to think about what information we need to get about the characteristics of this vaccine. If this is a stopgap vaccine that bears little, if any, relationship to the vaccines that are going to really carry the load in a pandemic situation, then that's one thing. If it's very closely -- if it's the same vaccine, then the answers to that question are perhaps different, so it's --

DR. BAYLOR: Well, I think we, and Robin from the Department can answer as well, but when you look at this, you have to look at where we are in time. The 600 million doses, I mean it depends on where you are. I mean we know that there are numerous vaccines under development that are potentially better, if you will, than this vaccine. This is an interim vaccine.

Depending on where those vaccines are in development, those vaccines -- some of those newer vaccines, the adjuvanted vaccines or what have you, those may be the vaccines that we use to hit the magic number of the 600 million doses.

But again, it just depends on how fast those vaccines are developed, how fast those clinical trials are done and what the data suggests or support for those vaccines.

So again, today we're -- what we're faced with is this vaccine that requires two doses and at 90 micrograms. That's where we are today. A month from now, a year from now, five years from now, we could have -- we probably will have additional products that we hope that are going to be better. You're still not clear?

DR. SELF: Well, to get information about effectiveness of this vaccine, we're probably going to be in the early stages of the pandemic? I mean we're

not going to get that probably from the high risk groups? I'm just guessing because it's still not clear to me who those high-risk non-pandemic vaccinees would be. And that implies a certain timing of events then.

There is, you know, only a handful of months between the first opportunity to get effectiveness information about this vaccine and the 600 million doses or, you know, whatever the next wave of response is. And so, again, I'm -- the charge here is what studies, you know, should be done to characterize the effectiveness of this vaccine. And I'm wondering -- there are limited opportunities for that, and I'm trying to figure out what information would be critical and could be used in how this unfolds so I could, you know, answer that question.

DR. GOODMAN: Yes. I think that the likely -- you know, this is an interim preparedness measure. There's also -- you

know, although we're all very optimistic about reports and information we receive about potentially more immunogenic vaccines, we always have to see that data. And particularly with things that haven't been used in hundreds of millions of people already, we have to be concerned that the safety database is adequate before a completely new technology is widely used.

Now all that said, what HHS has been encouraging is rapid development of that information from a number of manufacturers, and FDA is encouraging that we get that data as it becomes available so that in an emergency -- we're going to be in a situation -- we are in a very dynamic situation right now. Every six months, we learn a lot more. That's one of the good things about this, because there's a lot of information about flu vaccines that is being developed that is informing us. But it's also one of the big challenges and it's a

challenge in making a static risk-benefit decision.

But what I was going to say is that so let's say there were a pandemic tomorrow, six months, two years. What we're going to do is look at all the data that are available out there, probably seek advice also about that data from people like yourselves -- where are we at that moment, what is the snapshot, and then what are the alternatives for trying to provide protection, you know, to the American people.

Right now today where this vaccine is and the use that's being proposed is that in a situation perhaps where human-to-human transmission is beginning to occur or we see people who may have high risk of exposure to H5N1 that this vaccine would be available for use under license, and getting -- you know, and obviously the amounts of this vaccine because of the technology are

going to be somewhat limited. It's going to be what's in the stockpile. I think getting to your original question, what's important, and to CDC's presentation, is it will be good to be able to evaluate field efficacy of that vaccine. It may be more or less efficacious than expected, and that early information may inform decisions about further production, etcetera.

I think certainly there's a likelihood there could be a drifted strain or a different clade as discussed and that probably, you know, you wouldn't want to produce that even if it was with this technology.

So the real question is, and this gets back to, I think, your question about the modeling, and in my presentation later, I have a slide about that, but I think you don't want to make too much of models, but they have many, many assumptions. But part of what drives this is the historical

experience with flu which is that some immunity can have an affect, even limited immunity. And then in these models, for example, suggest that if you achieve 30 percent protection even and even with 1 dose of such a vaccine, that there may be, in certain circumstances, combined with other measures, significant affects on a pandemic.

So the real question is here's a vaccine based on a known technology -- it is somewhat different; it's a higher antigen does; it's a unique antigen, but can this provide at present the potential for benefit in this situation, and it's a fluid situation.

But I think input on how CDC and FDA should help evaluate efficacy early in a pandemic would be helpful. And I also take Dr. Couch's point. And you heard from both the CDC and FDA presentations, there's a lot of concern for how do we improve monitoring the safety and communication about safety

early in a pandemic, and we're trying to exercise those systems with annual influenza vaccine as well.

DR. KARRON: Dr. Stapleton?

DR. STAPLETON: I think I'm struggling with what several others have alluded to or directly mentioned, but I guess for Dr. James and perhaps Sanofi Pasteur, I have one question and one comment. How can we come up with a better definition of high risk group? I think it seems very vague and unclear, and that's going to be a key issue in a stopgap measure. If it's beginning of pandemic, if it's pre-pandemic, if it's -- how are these definitions made? And I think they should be made.

And secondly, post deployment monitoring, I think that's one of our charges is to address that. It seems to me that there really have to be plans in place to compare not only unvaccinated and

vaccinated individuals but also comparison of the people who are vaccinated with seasonal vaccine as a comparison group. And I think that's something that should be looked at for cross-protection or priming for future vaccines.

DR. KARRON: Dr. Hetherington?

DR. HETHERINGTON: Dr. Webster earlier said this is an historic vaccine in more than one way -- sorry, my microphone doesn't seem to be working --

Dr. Webster earlier said this is an historic vaccine in more than way, and I think what I sense we're all struggling is the roadmap to where this vaccine is going. We're at a starting point, but it's not clear what the evolution is in front of us. For instance, one of the questions to us is what additional studies should be done to assess the efficacy of this vaccine. Well, if the roadmap is to replace this with a new clade vaccine in the next 6 to 12 months,

I'm not certain that we can justify any resource going into any additional efficacy studies, while safety certainly should be continued to be monitored. So it's not really clear to me that that has been laid out to the committee as a whole as to where this fits into the entire evolution of vaccines for this specific purpose.

We're told that this is going to be for first responders, but there is also an indication up there for primary vaccination of healthy adults which speaks to a much broader population, and it's not -- wasn't clear to me, at least, in the presentation that that was really something for which we should be considering this vaccine. It looked like there was more of an evolution to it. I wonder if somebody might address that?

DR. HACHEY: One group that's likely to receive this vaccine, in part because DoD does have a smaller stockpile

than HHS, but nonetheless we do have a small stockpile of the 1203 (clade 1) vaccine. And we are probably likely to be included eventually in the national strategy as far as the larger stockpile that will be evolving over time.

DoD has some unique attributes that we have built into our immunization programs already that all of our active duty members which represent that healthy kind of middle-age-younger-age group, every vaccine that they do receive, whether it's influenza, anthrax, or in this case, a pre-pandemic or a pandemic vaccine, is already monitored. So we do have a tracking system already in place as well as a tracking system to monitor for adverse events. We have also established a system that could be easily adaptable to monitor, again, ongoing adverse events and efficacy of the vaccine.

So DoD is in somewhat of a unique niche in that we're likely to use the

vaccine should a pandemic be imminent. We have some already in hand, and we do have tracking mechanisms that are either already in place or easily adaptable to monitor the outcomes that are currently of interest.

DR. KARRON: Dr. James, did you also want to respond?

DR. JAMES: Yes. I just wanted to clarify the third question that we are asking for is really on if the vaccine is licensed post use. So post licensing use of the vaccine, what sort of effectiveness and safety data you would like to see, you would like collected. Okay? So it's not necessarily unless you believe that the data presented are not sufficient to license it, then, of course, you can speak on additional studies that you believe need to occur. But that question is specifically for if the vaccine is licensed and it is used, how do we go about collecting effectiveness and safety data.

DR. KARRON: If I can maybe clarify or amplify your question, Dr. Hetherington. I think you were asking not so much that as perhaps where does this fit into the pipeline of vaccines that are going to come before the FDA to help us understand given that everybody admits that this is a stopgap vaccine, to help us plan what kinds of post licensure test, if this vaccine were to be licensed, should be done. Is that -- did I say that correctly?

DR. HETHERINGTON: I think the FDA spokesperson was correct in that I did misread the question, but I think the larger question was exactly as you said. What is the overall roadmap for this approach.

DR. KARRON: Dr. McInnes?

DR. McINNES: Thank you, Ruth. I'm struck by these conversations that we don't seem to have a real advocate for this vaccine, which is an unusual circumstance coming before the FDA Advisory Committee.

We don't have a manufacturer of a product that intends to market this commercially, and all those incentives that go with that are not in place. And so I think we have to take a little bit more pragmatic view here with all of this uncertainty. And I think we do have a vaccine here. It is immunogenic. It's not as immunogenic as we'd perhaps like to see. It uses a lot of antigen. It's a -- you have to have two doses which is very inconvenient. But it is a vaccine.

And the safety profile in the small numbers that have been put before us, I find somewhat comforting. I think it's acceptable. Of course, we'd like more data but I think it looks quite good at this particular point in the small numbers.

I think all of the uncertainty tracks around the concern that, you know, a recommendation to license, and we don't understand how the product will be used, by

whom, when, where. We normally have a vaccine manufacturer who is manufacturing bulk lots of vaccine, not just one, who is marketing product, it is getting used, we're continuing to gather data, which then provides the basis for a community assessment of whether this is safe and efficacious, and we're not going to have any of these readouts. We're not going to have any of these signals coming in this situation.

And so -- yet the option on the table is to look at licensure for a product, and we understand licensure and use in a completely different framework normally. So I am left -- I am struck -- you know, Sanofi does not propose to conduct further studies to gather data, and I understand that they were a contract manufacturing in this situation. They have no commercial market. I'm not sure I totally understand why there isn't a potential commercial market, but

that's apparently not their plan.

So I'd like to understand a little bit more from the Department about a very clear articulation of use of this product, when, where, how, decision making. And I'd like ask for some guidance from the FDA about what options they have to manage not only the license but the use of the vaccine, because I think once it's licensed, it sits there with that. And I'm trying to understand the options for management of this package which is very unusual.

DR. KARRON: Bruce?

DR. GELLIN: Pam's laid out some important principles and questions. There's also been a discussion about 20 million, 600 million, where the vaccine sits, so I think that we need to remember that this was created for the stockpile.

And it's also important to remember that when we started doing this, the idea of stockpiling an influenza

vaccine, if you, you know, rewind the clock and look at what the doctrine was at the time, nobody was stockpiling influenza vaccine because you know the virus would change and you had to keep up with it.

So the idea that you would go into creating stockpiles knowing that the virus would now do what it has shown it is going to do was where we got into this, but the idea was that a stockpile could provide some protection.

I would think, importantly, early on we also recognized that going through all this was going to provide a lot of experience to a lot of people that we didn't want to learn in the time of an emergency. That's separate from the discussions here, but what we have now is vaccine that's created for a stockpile.

As you've seen from Robin's slide, accumulating enough to hit the national target of enough vaccine for 20

million people is not easy given that your - essentially we refer to this as - you know, we're asking the manufacturers to use every available minute of their off season production. So the slid that Robin showed shows how you can only get incremental amounts of that to be able to put that vaccine into a stockpile. And then we have the issues of time that -- of what happens to this vaccine over time, what happens to the virus over time. So we have -- so the 20 million goal was set as a construct to have something at the beginning of a pandemic that you might use that would provide some protection to people on the front lines while you were then creating the better vaccine that was tailored to the circulating virus.

So the piece that was in -- so I'll draw on two different slides -- so I think that Norman ended with his final bullet was the benefit of having a licensed

vaccine against a potential influenza virus strain weighed against the risk of having no vaccine. So that's an important principle.

The other piece was embedded within David Shay's slides that while he talked a lot about the process for revisiting the pandemic vaccine prioritization, there's a separate process done by the same interagency group to take a hard look at that if we had to use it today, how we would use the existing vaccine and then up to 20 million doses -- 20 million people, what kinds of people would those be. So I don't have a clear answer now. There is a pretty vigorous interagency process that's defining that at the same time its defining the priority list broadly, but that's the construct here.

Again, I think it's been signaled in many of these slides. It is front line, critical infrastructure that constitutes those 20 million, but I can't give you more

precision until there is clear guidance on who those people are.

DR. KARRON: I do want to follow-up on Pamela's question, though. So does that suggest then that the 20 million doses in the stockpile, it would be used for first responders, who those people are is to be defined, but it would not be used for populations other than first responders?

DR. GELLIN: That's the goal of the stockpile recognizing it was a finite amount and that you would then -- we have the larger goal that Robin can talk more about of creating a production capacity so you would have enough for the larger population.

DR. KARRON: A production capacity with this vaccine?

DR. GELLIN: For the vaccine that you needed, that you have to determine at the time. I mean, again, I think that the general idea was that they -- this quote

pre-pandemic vaccine was the best you could make based on the viruses that were circulating at the time that then might give you somewhat of a match with the idea being that you would likely have to have a different vaccine for the pandemic --

DR. KARRON: I just have a particular question for the FDA that has to do with their draft guidance, because obviously this stopgap vaccine, if you will, does not meet the criteria -- some of the criteria set forth in the draft guidance. Will licensure of this vaccine, if it is licensed, have any impact on the draft guidance or not?'

DR. BAYLOR: I'll answer that. I mean, in essence, no, this vaccine was -- these clinical trials were done prior to these guidances. The guidance documents will be applied to forthcoming vaccines, but I think we have to look at the type of vaccine we're dealing with. Here we're

looking at a vaccine that's been manufactured by a licensed process. If another vaccine comes forward with a U.S. licensed process, more than like, it will be evaluated the same way. That guidance document will apply to vaccines, in particular the pandemic guidance will be applied to the vaccines that are coming henceforth.

DR. KARRON: Dr. Wharton?

DR. WHARTON: Understanding the need to get these doses manufactured as quickly as possible and the need to get as many doses as possible out of the antigen that could be made, I'm assuming that this is preservative-containing vaccine in multi-dose vials. My question regards that formulation. Given that the 90 microgram dose, I believe, is a 1-mil dose, from what was said early, should I -- is it correct that those two doses administered would contain 100 microgram of mercury thimerosal

preservative in those two doses?

DR. JAMES: I'm being told we -- yes, we believe that that's accurate, but if Sanofi can confirm that.

DR. LEE: Hi. I'm Dr. Sam Lee representing Industrial Operations for Sanofi Pasteur. Yes, the 1-mL vaccine does contain 100 micrograms per mL of thimerosal and the vaccine would contain that 100 micrograms.

MS. KRIVACIC: Given that it contains the thimerosal and we're looking at annual flu vaccinations, what is the risk of exposure of thimerosal from your annual vaccinations as well as this, you know, stockpile? If you can kind of comment on that in terms of the exposure of thimerosal?

DR. LEE: Right. I'm not sure I'm the right person to answer that.

MR. HOSBACH: Hi. I'm Phil Hasbach, Government Policy and Government Relations for Sanofi Pasteur. In terms of

our seasonal flu vaccine, we have a variety of formulations available, some of it unpreserved with no thimerosal at all, and of course others with multi-dose vial. It's really constrained by our filling and finished capacity for single-dose syringes and single-dose vials. So for the traditional multi-dose vial vaccine, it has 25 micrograms of preservative -- of preservative in it, thimerosal.

In this instance, we're looking to produce as much vaccine as possible to get it into the arms of citizens as quickly as possible, and right now with the fill and finish capacity that manufacturers have, especially Sanofi Pasteur, it's optimal to do it with multi-dose vials and using a preservative.

MS. KRIVACIC: I had a question for Dr. James. On the studies that you were looking at with the pediatric population, was there any indication of those that were

previously vaccinated with the annual flu vaccination, the seasonal flue vaccination that had thimerosal and then this particular flu vaccine?

DR. JAMES: In terms of the pediatric studies, I will ask the NIH to address that. The pediatric data has not been submitted to the BLA.

MS. LOWERY: So with the pediatric trial in which we evaluated two doses of the 45 microgram vaccine or an optional third dose of the vaccine, we did collect information on children who had previously received the TIV or the inactivated vaccine and also on if they had received FluMist, but we did not specify if the inactivated vaccine that they had received that, trivalent inactivated vaccine did or did not contain thimerosal.

DR. KARRON: Dr. Gellin?

DR. GELLIN: I think this is a manufacturing question. We often hear about

that the switch to multi-dose vials to single-dose vials can translate into numbers of doses that can be lost because of, I don't know exactly why, some of it sticks to the side or whatever, but you have to do some overfilling of each vial so, therefore, that adds up. Given the slide that Robin showed of how difficult it is to even accumulate the targets we're going for, can you give us a sense of -- do you know what the math is, what the calculation would look like if you went from the number of multi-dose vials, how many single-dose vials would you have?

DR. LEE: Switching from multi-dose to uni-dose vials, actually, there's probably a twofold answer to that. It's problematic in two ways. One is certainly, as you said, the filling capacity. The actually filling rates are significantly different for a multi-dose versus a uni-dose vial because just the number of vials that

you're dealing with. In this case, we're talking about a five dose per vial, 5 mL's in a single vial verus a uni-dose where there's 1 mL per vial. So the filling rates right there, you're taking five times as long to fill the same number of doses.

The second is just the sheer practicality of needing to handle so many vials for distribution and use. In a pandemic situation, you're talking about distributing 300 million, 600 million doses. You're talking about 300 million, 600 million vials versus. If this is a 5 mL dose or I'm sorry a five dose vial, you're talking one-fifth the number of vials. So those -- kind of a twofold aspect.

In terms of the actual overfill and what you have addressed there, there is a slight difference in terms of need to overfill of uni-dose vials, and it could be fairly significant on the order of 10 to 20 percent.

DR. KARRON: Dr. Krivacic?

MS. KRIVACIC: I just had one other question or comment. I guess I understand we don't have a lot of time here with regard to, you know, dealing with a pandemic, but I think it would be very important to understand what the effects of an annualized flu vaccine with thimerosal plus the avian flu vaccine, what kind of effect that would have on a woman of childbearing potential. That would be my concern and I think that's a concern you may get from the general population down the road so just a sort of an FYI.

DR. KARRON: Dr. Jackson?

DR. JACKSON: I guess this is a question for FDA. I'm struggling with the obvious limitation of having a study data set of 100 people who've received the recommended dose regimen and it being asked to go forward for licensure which is a very, obviously, unusual situation. With that

number of people, I mean we're not able to exclude the possibility there are, in fact, quite common adverse events that we're not detecting in the original trial. And this is a vaccine produced by established methods.

However, it's got 12 times the amount of strain-specific antigen as the usual seasonal influenza vaccine course, so I think that leaves open a possibility that there could possibly be something unexpected when 90 micrograms is give twice.

In addition, we know very little about, as I said before, any sort of subsets, potentially important subsets, such as age within that group, and we probably can't learn a lot more given the small sample size.

So it would seem like a relatively straightforward and limited scope study could be attempted along the lines of a, you know, traditional immunogenicity

safety study that would provide more information to reassure us about this particular vaccine and perhaps also to provide some suggestion of where the vaccine should be targeted given that the supply will be limited and we want to avoid targeting groups for whom the vaccine was unlikely to be very effective at all if there was heterogeneity in the response by personal characteristics.

So I wonder if the FDA could just tell us more about sort of why we are where we are now in regard to that.

DR. BAYLOR: When you say where we are now in?

DR. JACKSON: Why does it -- I mean I'm just curious as to why we seem to be restricted to looking at a data set of 100 people without an option for a more expansive assessment of immunogenicity and safety prior to moving forward with the important step of licensure.

DR. BAYLOR: Again, I'd go back to my point, and I understand your point about the manufacturing process. And if we go back and look at the process, as I mentioned earlier today, for strain change, and we would not require clinical data, we do not require clinical data for changing the annual strain. This vaccine is manufactured by a licensed process.

Granted there is more antigen here, although you are receiving 45 micrograms for -- although it's a single dose, you do receive 45 micrograms in the seasonal, so it's a 15. It's a 45 versus a 90 times 2.

And we believe that the -- you know, that we admit -- we recognize that the data are limited, but I think we really have to keep a perspective what the aim here. We're saying -- there are -- there is no licensed U.S. vaccine for an H5N1 strain. We have a limited amount of data but with a

product that is manufactured by a licensed process. And so we believe this data would be sufficient to be submitted for the evaluation for licensure in the case of, as we said, during a pandemic or, as we've said, individuals who may likely be exposed to an H5N1 or go into a region with an H5N1 as we've heard from our colleagues from the DoD.

So, yes, the data are limited but we -- the data are supportive -- I believe the data is supportive of at least demonstrating that this vaccine, based on the licensed manufacturing process, doesn't elicit any undue concerns. But that's what we're asking you. We're asking you based on this limited data set, what are your recommendations.

I mean we really want to know your comfort level in using this vaccine that's been studied in a limited population but considering how this vaccine will be

used and when it will be sued and the fact that this vaccine is -- will not be commercialized. This vaccine will not, more than likely, be distributed to the entire population in the country. So within that realm, we're asking you for your opinion and recommendations and advice.

DR. KARRON: Dr. Couch first, then Dr. Farley.

DR. COUCH: I guess I just generally want to speak for supporting this, and a lot of what we would like to have, I'd say, I'm not sure that I would strongly recommend using the resources that would be necessary to get it. I think -- I don't know a whole lot about the H flu vaccine -- H5 vaccines that are out there, but there are others coming along. And if you read the press reports, they're going to be better than this.

But this is the vaccine we have before us for licensing, and if you're a

practicing physician, there's a whole lot of difference in using a licensed preparation and using an unlicensed preparation and even unapproved use. And so this is -- I would think of this almost as a step one. This is not the solution to the H5 vaccine problem, but a step one in moving that direction.

And I would also like to put in the point that I would strongly support keeping the five-dose vials, because that gives us flexibility. You see? And if -- I would not be unhappy at all as the physician if I was required to make this my first priming dose to be followed by the clade 2 vaccine if that's the supply required me to make that kind of decision and use it in that way so that we've got an approved preparation that is less than desirable to what you're hearing a lot about around this table, and nobody would differ with that. There are other preparations that are coming along that the press reports say are better,

and there's actually some of it published.

But this is a step one to move us in that direction. And Dr. Baylor has been saying, you see, this data is with a preparation that is using a manufactured processed, and it is an immunogenic preparation, and we don't know how good it -- we know it'll work. We just don't know how good it will be.

DR. KARRON: Dr. Farley?

DR. FARLEY: Well, I just wanted to comment that, in response to Dr. Couch's statement, that I think physicians are much -- they have a comfort zone of using a licensed vaccine because it has gone through a rigorous standardized process that has, you know, set, you know, a high standard. And I think that we would probably all agree that this is a special circumstance quite different from our usual rigorous high standards and high expectations. And that's sort of the issue here, and that is, you

know, is there any mechanism for licensure that is, you know, has some sort of qualifier that it is licensed for non-commercial use in special circumstances. I mean are there different levels or circumstances. Or in our pandemic planning, should we be setting some policy that would allow for -- you know, that we are -- we would be designating this?

I mean otherwise, our concern is that we're licensing it and it's just licensed like every other vaccine and we've given it a seal of approval that says it met, you know, a standard that I'm not sure we're able to say here but we understand why. And I'm supportive of the idea of having the stockpile and being prepared, but the standard of licensure is this question of are there gradations.

DR. KARRON: Dr. Webster, did the FDA want to say anything in response to that or? No. Okay. Dr. Goodman?

DR. GOODMAN: Yes. I -- you know, one comment I would make is that the original concept here is this vaccine was developed. I mean the thing that is different about this vaccine, every year a new influenza vaccine is made using this process by this manufacturer. And, you know, tens of millions of doses are used. And there's a very well-established record there.

So what's -- in fact , the original intent is that if somebody used a licensed manufacturing process -- and in the original draft guidance -- that we would require some clinical data to be -- establish the dose and immunogenicity but it wouldn't necessarily require a new license. Okay. The issues here are that dose is somewhat higher, but there was not an anticipation that this is as if this is an entirely new vaccine So I think it's important to put that out there. Because it

is intended for this specific use, because it could potentially be available when an annual vaccine is available, and it's a different indication, it's gone down the pathway of having -- being proposed for a separate license.

But, you know, just to sort of share our view of what this all came from. So it's not that this is sort of this new product in a vacuum and we're saying just consider it based upon 100 patients of something like this, but this is really a modification of a well-characterized product.

But that said, you know, I'd also like to point out that on -- I mean I think we're here to hear these concerns, and if there's a feeling that additional patients would add to the comfort level here, we should hear that.

But one comment I would make is that, for example, in 1976 with swine flu