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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

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MEETING

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TUESDAY,
FEBRUARY 27, 2007

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The meeting convened at 8:00 a.m. in Salons A, B, and C of the Hilton Washington D.C. North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Ruth A. Karron., Chair, presiding.

ADVISORY COMMITTEE MEMBERS PRESENT:

RUTH A. KARRON, M.D., Chair
ROBERT COUCH, M.D., Temporary Voting Member
NANCY COX, Ph.D., Non-Voting Member
THEODORE EICKHOFF, M.D., Temporary Voting Member
MONICA M. FARLEY, M.D., Member
BRUCE GELLIN, M.D., M.P.H., Temporary Voting Member
WAYNE HACHEY, D.O., M.P.H., Temporary Voting Member
SETH HETHERINGTON, M.D., Industry Representative
LISA JACKSON, M.D., M.P.H., Member
SUSAN KRIVACIC, Patient Representative

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PAMELA McINNES, D.D.S., Temporary Voting Member
JOHN MODLIN, M.D., Member
CINDY PROVINCE, R.N., M.S.N., M.A., Temporary Voting Member
STEVEN SELF, Ph.D., Member
JACK STAPLETON, M.D., Member
JOHN TREANOR, M.D., Temporary Voting Member
ROBERT WEBSTER, Ph.D., Temporary Voting Member
MELINDA WHARTON, M.D., M.P.H., Temporary Voting Member
BONNIE WORD, M.D., Member

FDA PARTICIPANTS:

CHRISTINE WALSH, R.N., Executive Secretary
NORMAN BAYLOR, Ph.D., Director, Office of Vaccines Research and Review
ROBERT BALL, M.D., M.P.H., Sc.M., Vaccine Safety Branch, Division of Epidemiology, CBER
JESSE L. GOODMAN, M.D., M.P.H., Center for Biologics Evaluation and Research
ANDREA N. JAMES, M.D., Division of Vaccines and Related Product Applications
JOSEPH G. TOERNER, M.D., M.P.H., Vaccine and Clinical Trials Branch, DVRPA

SPEAKERS:

PATRICK CAUBEL, M.D., Ph.D., Sanofi Pasteur
KENNETH P. GUITO, MBA, Sanofi Pasteur
PHILIP HOSBACH, Sanofi Pasteur
LINDA C. LAMBERT, Ph.D., Division of Microbiology and Infectious Diseases, NIAID, NIH
ROBIN ROBINSON, Ph.D., Acting Associate Director, HHS/ASPR/OPHEMC
DAVID K. SHAY, M.D., M.P.H., Centers for Disease Control and Prevention
JOHN TREANOR, M.D., University of Rochester Medical Center

PUBLIC SPEAKERS:

MANON COX, Protein Sciences
BRUCE INNIS, GlaxoSmithKline

I-N-D-E-X

I-N-D-E-X (Continued)

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

DR. KARRON: I'd like to call this meeting to order if everyone would please take their seats. And I'd like to ask Ms. Christine Walsh to make some announcement.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting of the advisory committee. Today and tomorrow's sessions will consist of presentations that are open to the public.

I would like to request that everyone please check your cell phones and pagers to make sure they are off or in the silent mode.

I would also like to request that any media inquiries be directed to either Heidi Rubello (phonetic) or Karen Reilly (phonetic) from FDA Office of Public

Affairs, Karen and Heidi.

I would like to read into public record the conflict of interest statement for today's meeting. The Food and Drug Administration, FDA, is convening today's meeting of the Vaccines and Related Biological 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 U.S.C. 208 and 21 U.S.C. 355(n)(4) is being provided to participants in today's 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 including but not limited to 18 U.S.C. 208 and 21 U.S.C. 355(n)(4). Under 18 U.S.C. 208, applicable to all government agencies, and 21 U.S.C. 355(n)(4), applicable to certain FDA committees, congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individuals services outweighs his or her potential financial conflict of interest, Section 208, and where participation is necessary to afford essential expertise, Section 355.

Members and participants of the committee who are special government employees at today's meeting including special government employees appointed as temporary voting members have been screened for potential financial conflicts of

interest of their own as well as those imputed to them including those of their employer, spouse or minor child related to Topic 1, Discussion and Recommendation on the Safety and Immunogenicity of an H5N1 Inactivated Influenza Vaccine sponsored by Sanofi Pasteur; Topic 2, Discussion of Pandemic Influenza Vaccine Strategies and Clinical Development of Pandemic Influenza Vaccines; for Topic 3, Discussion and Recommendations on the Selection of Strains to be Included in the Influenza Virus Vaccine for the 2007-2008 Season; for Topic 4, Discussion of Influenza B Strain Including the History of B Strain Circulating Lineages.

Financial interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment. Today's agenda involves a discussion and

recommendation of the safety and immunogenicity of an H5N1 inactivated influenza vaccine.

In accordance with 18 U.S.C. Section 208(b)(3), waivers were granted to Dr. Robert Couch, Dr. Lisa Jackson, Dr. Ruth Karron, Dr. John Modlin, and Dr. Robert Webster. Dr. Bruce Gellin and Dr. Wayne Hachey have been fully screened for conflicts of interest under usual procedures and have been advised that there are no financial conflicts of interest that would preclude participation or voting in this meeting or that might require a waiver under relevant statutes and regulations.

I note, however, that Dr. Gellin is involved in the process of pandemic vaccine procurement for the Office of Secretary of the Department of Health and Human Services in his capacity of Director of the National Vaccine Program Office. To avoid any perceptions of inappropriate

influence in the actions of this committee, Dr. Gellin will not be voting on Topic 1. Dr. Hachey, who is director of Deployment, Medicine and Surveillance for the Department of Defense and whose office has responsibilities for procurement, likewise, will not be voting on Topic 1.

For the discussion of Topic 2 on Pandemic Influenza Vaccine Strategies and Clinical Development of Pandemic Influence Vaccines, Dr. John Treanor received a waiver under 18 U.S.C. Section 208(b)(3). Dr. Treanor will not participate in the discussion of Topic 1. For Topic 1, Dr. Treanor will serve as a guest speaker making a presentation. Dr. Treanor is Professor of Medicine, Infectious Diseases Unit, at the University of Rochester Medical Center. He will present data related to Topic 1 on behalf of NIH.

With regard to FDA's other guest speaker for Topic 3, the agency has

determined that the information provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments. Mr. Albert Thomas is employed as Director, Viral Manufacturing, Sanofi Pasteur in Swiftwater, Pennsylvania.

Dr. Seth Hetherington is serving as the industry representative acting on behalf of all related industry and is employed by Icagen, Inc. Industry representatives are not special government employees and do not vote. In addition, there may be regulated industry 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 the FDA for conflict of interest. This conflict of interest statement will be available for review at the registration table.

We would like to remind members and participants that if the discussions involve any other products or firms not already not 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 a sponsor, it's product and, if known, its direct competitors.

Thank you. Dr. Karron, that ends the conflict of interest statement, and I turn the meeting over to you.

DR. KARRON: Thank you, Christine. I'd like to welcome everybody to

this VRBPAC meeting for what promises to be a very interesting two-day discussion on seasonal and pandemic influenza vaccines. I'd like to begin by going around the room and having all of the participants introduce themselves. I'll start with Dr. Modlin.

DR. MODLIN: This is John Modlin from Dartmouth Medical School.

DR. COUCH: Robert Couch, Baylor College of Medicine.

DR. FARLEY: Monica Farley, Emory University School of Medicine.

DR. SELF: Steve Self, Hutchinson Cancer Center.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. WHARTON: Melinda Wharton, Centers for Disease Control and Prevention.

MS. KRIVACIC: Susan Krivacic, Patient Representative, Austin, Texas.

DR. HETHERINGTON: Seth Hetherington, Icagen, Inc., Research

Triangle Park, North Carolina.

DR. WORD: Bonnie Word, Baylor College of Medicine.

DR. JACKSON: Lisa Jackson, Group Health Center for Health Studies.

DR. GELLIN: Bruce Gellin, Department of Health and Human Services.

MS. PROVINCE: Cindy Province, Acting Consumer Representative, Center for Bioethics and Culture.

DR. STAPLETON: Jack Stapleton, University of Iowa.

DR. HACHEY: Wayne Hachey, Department of Defense.

DR. WEBSTER: Robert Webster, St. Jude Children's Research Hospital.

DR. McINNES: Pamela McInnes, National Institute of Dental and Craniofacial Research, National Institutes of Health.

DR. JAMES: Andrea James, FDA.

DR. BAYLOR: Norman Baylor, FDA.

DR. GOODMAN: Jesse Goodwin, FDA.

DR. KARRON: And I'm Ruth Karron from Johns Hopkins University. Our first speaker will be Dr. Norman Baylor from the FDA.

DR. BAYLOR: Good morning. I'm Norman Baylor. I'm the Director of the Office of Vaccines Research and Review at the FDA's Center for Biologics Evaluation and Research. Today I'm going to provide a brief overview, set the stage for today's meeting, in particular this session on our discussion of the BLA for Sanofi Pasteur's H5N1 vaccine.

Today we'll be presenting data in support of the first Biologics Licensed Application for a vaccine against H5N1 influenza viruses. This vaccine was manufactured by Sanofi Pasteur using the same manufacturing process as used for their licensed seasonal vaccine. The safety and immunogenicity data for the H5N1 strain were

derived from a clinical trial completed by three National Institutes of Health Vaccine Treatment and Evaluation Centers.

As most of you know, there are currently no human vaccine licensed in the United States for avian influenza viruses such as H5N1. We at the FDA are working with our partners in the Government such as the National Institutes of Health, the Centers for Disease Control and the Department of Health and Human Services as well as the vaccine industry to facilitate the licensure of safe and effective vaccines for the use against potential pandemic influenza strains.

We're also trying to facilitate the evaluation of vaccines for potential use in the period prior to a pandemic including the potential uses for priming and cross-protection against evolving strains. And you will hear more about this in the discussion following this session.

We know that the risk of a pandemic is serious. H5N1 is present in large parts of Asia as well as now in the continent of Africa, Nigeria, Egypt. There is increased risk that more human cases will occur. The continuing presence and spread of the virus to new areas in poultry and wild birds increases the opportunities for human cases to occur. And we know that each additional human case provides this virus with an opportunity to improve its transmissability in humans and thus develop into a pandemic strain.

The timing and severity of the next pandemic we cannot predict. However, the probability that a pandemic will occur has increased and vaccines will be an important intervention against pandemic influenza and there are modeling studies that suggest that even a single dose of a vaccine of limited effectiveness may have significant effects early in a pandemic and

reducing illness and spread of the virus.

I show this slide -- this is a cumulative number and I don't know if you can see this from the back, but the important thing is these two numbers. It's a cumulative number of confirmed human cases of avian influenza from H5N1 reported by the WHO last week. And as I said, the important thing here is as of February 19th, there were 274 cases. I believe there's 278 now. And of this 274, there have been 167 deaths which you can't see, but there are a variety of countries, as I mentioned before, Asia and the continent of Africa.

So as a background to the product we're looking at today, as I said before, this product uses the same manufacturing process as the licensed seasonal influenza manufactured by Sanofi. For U.S. licensed seasonal vaccines, no clinical data are required to substitute new strains into the vaccine such as we call a strain change.

The clinical data for Sanofi's H5N1 vaccine is designed primarily as a dose ranging study. And as a result, you'll note today that these data are limited. The immunogenicity was evaluated in the clinical studies. The proposed indication from the firm is for individuals 18 to 64 years of age for use during a pandemic or for those at high risk of exposure to H5N1. This vaccine will not be marketed commercially but is intended for the U.S. stockpile.

So in summary, we are bringing this vaccine to you today because we know the threat of an influenza pandemic is real and likely to continue. This vaccine that we're discussing today is intended to be an initial step to support preparedness and to facilitate a rapid early vaccine response. If licensed, this vaccine will become the first licensed vaccine available in the United States against an H5N1 strength.

The vaccine industry, in

partnership with the Departments of Health and Human Services, is pursuing other approaches intended to elicit enhanced immune responses and require less antigen. And these are vaccines, for example, formulated with novel adjuvants which will not be the topic of our discussion today. We'll save that for another day.

If and when vaccines such as those formulated with novel antigens are found to be safe and effective, they're likely to supplant the use of the vaccine in discussion today. But we have to keep in mind that the benefit of having a licensed vaccine available now against a potential pandemic influenza strain must be weighed against the potential risk of having no vaccine at the time of a pandemic.

So that's my brief introduction and I'll be followed by Mr. Ken Guito from Sanofi Pasteur unless there are quick questions for clarification for me.

DR. KARRON: Thank you. Mr. Guito?

MR. GUITO: Thank you, Dr. Baylor. Dr. Karron, distinguished members of the advisory committee, ladies and gentlemen, good morning. I am Ken Guito and I represent the Strategic Project Office at Sanofi Pasteur. Sanofi Pasteur is pleased to the opportunity, along with our U.S. Government to present the first pandemic influenza vaccine for licensure, the H5N1 Influenza Vaccine, A/Vietnam 2004 (clade 1) 90 microgram formulation. Sanofi Pasteur views this formulation as an important first step which is based on time tested manufacturing technology, and we believe this represents unprecedented successful public-private partnership to prepare our nation for the threat of influenza pandemic.

As a recognized leader in influenza vaccine development and manufacturing, the U.S. Government

collaborated with us to manufacture first generation H5N1 pandemic vaccines for clinical studies and stockpiling. Sanofi Pasteur has the only licensed U.S. manufacturing facility for inactivated influenza virus vaccines. We're also the largest manufacturer globally producing roughly half of the world's of influenza vaccine.

Our H5N1 vaccine development efforts have relied upon time-proven technology that have been licensed for inter-pandemic vaccine production for many years in the U.S. Sanofi Pasteur has extensive candidate vaccine efforts under development utilizing both traditional technology as well as novel cell-based production and adjuvant technologies. We are collaborating extensively with government agencies domestically and abroad.

Sanofi Pasteur's presence here today with the first pandemic vaccine

applicant demonstrates our sense of urgency and our commitment to prepare for a possible pandemic event. We and other manufacturers continue on our efforts to develop additional strains of vaccine each and improvement on the last.

The H5N1 unit dose material used in a DMID clinical trial 04-063 was produced in 2004 under Health and human Services RFP award with Sanofi Pasteur functioning as a contract manufacturer. You'll hear more this morning on the DMID 04-063 trial from Dr. Treanor from the University of Rochester and from Dr. James from the FDA and more on the influenza pandemic RFP process from Dr. Robin Robinson from Health and Human Services in subsequent presentations.

As noted by Dr. Baylor, Sanofi Pasteur submitted a biologics license application for the H5N1 influenza virus vaccine in October 2006. In 2004 through 2005, Sanofi Pasteur produced U.S.

Government stockpile doses of the same H5N1 clade 1 vaccine under subsequent HHS RFP awards. To date, in total, route 6 million 90 microgram-equivalent doses have been produced in the stockpile. It's important to note the majority of this vaccine is being held as a bulk formulation to allow longer shelf life and flexibility in subsequent formulation and in final packaging.

As Dr. Baylor and I have noted, the influenza virus vaccine, A/Vietnam 2001 (clade 1) 90 microgram formulation represents an important first in the response to influenza pandemic preparedness efforts. Sanofi Pasteur has a special responsibility and commitment to assist public health authorities in preparing for the possibility of a pandemic and to protect human health. We and other manufacturers, along with our Government collaborators, continue development efforts aimed at

bringing forward subsequent more advanced candidate vaccines that will allow us to respond in the event of a pandemic emergency.

It is now my pleasure to introduce Dr. Robin Robinson, Acting Associate Director, Public Influenza, Health and Human Services, unless there are any clarifying questions. Okay. Thank you.

DR. ROBINSON: Good morning, distinguished panelists and guests. We are here today to discuss the H5N1 vaccines that the HHS has brought together for stockpiling. What I'd like to discuss briefly with you this morning is the department's and the nation's strategic plans and goals, our program portfolio matrix to carry out those and achieve those goals, the stockpile requirements for the H5N1 vaccines, the H5N1 vaccine production where we are today, and finally have a few summary remarks on the H5N1 vaccine being

discussed this morning.

Why are we here today? Dr. Baylor has already alluded to that. In 1997, in Hong Kong, the city was hit with a poultry epidemic with high pathogenic avian influenza that wiped out many of the birds in the bird market and also crossed over into humans that were in contact with these infected birds. After cleansing and closure of these live bird markets, the epidemic was halted. However, in the winter of 2003 and 2004, H5N1 highly pathogenic avian influenza viruses re-emerged in water fowl and domestic poultry to cause an epidemic in Eastern Asia and also causing human deaths in Thailand and Vietnam.

In response to these events, the National Strategy for Pandemic Influenza was prepared and issued November 1, 2005. The President requested appropriations of $7.1 billion dollars of which $5.3 billion dollars has been appropriated thus far. In

this strategy, the department and the nation communicated the needs for vaccine, antiviral and diagnostic research and development, stockpiling of antiviral and vaccines and the communication of other infrastructure building for the vaccine industry to address pandemic preparedness and response needs.

From that strategy, an implementation plan was prepared and issued in May of 2006. In this implementation plan, there are over 300 action items that the departments within the U.S. Government and the individual agencies within each department are responsible for implementing this pandemic preparedness and response actions. It provides guidance for each of these items and it defines the specific roles, responsibilities, metrics and timelines for accomplishing these action items. Further, it communicates to other non-federal entities including state and

local governments, industry and even personal actions that can be taken for pandemic preparedness and response.

Also, within the pandemic strategy and implementation plan is, where possible, the use of licensed antiviral drugs and vaccines. From the strategy and implementation plan, there are a number of goals that have been enumerated. I draw your attention to two of these goals for vaccines. One is to establish and maintain a dynamic pre-pandemic influenza vaccine stockpile available for 20 billion persons in the critical workforce including first responders. Secondly, and built onto that, is to provide pandemic vaccines for all U.S. citizens within six months of the onset of a pandemic and, therefore, if a pandemic vaccine is two doses per person, that would mean that we need 600 million doses.

How did HHS try to accomplish and account for these goals? Well, we've

developed an approach that was considered a program portfolio matrix, and I draw your attention to this approach for vaccines, antivirals and diagnostics and the areas of advanced development, stockpiling acquisitions and infrastructure building. Specifically, for this particular discussion, H5N1 vaccine stockpiles were established and developed in association with our sister agencies, the NIH, CDC, FDA and our industry partners that are U.S. licensed influenza vaccine manufacturers.

In 2004, we set out to establish these stockpiles giving industry the experience necessary to produce these vaccines at commercial scale, and we had a number of requirements to establish and maintain this stockpile. First, that it should be fore 20 million persons in the critical workforce including the first responders. Second, it would be for the usage at the onset of an H5N1 virus pandemic

prior to the release of a well-matched pandemic vaccine. Thirdly, that this vaccine stockpiling manufacturing should be done without disrupting seasonal influenza vaccine manufacturing campaigns. Fourth, usage of apathogenic reassortants of high-risk virus strains as virus reference seeds were mandated for this manufacturing and that the manufacturing should be done at influenza vaccine sites, because these sites are the professionals at making influenza vaccine, and they use the commercial scale manufacturing process for the licensed inactivated split monovalent influenza vaccines. Therefore, as Dr. Baylor said, it would be a strain change for an antigen alone vaccine.

This vaccine, as already pointed out, is stored both as bulk and final container vaccine, and stability testing has been ongoing since September of 2004 when the first contracts were let. Further, by

most of the vaccine being involved form, we're able to formulate the final container vaccine as antigen alone or with adjuvant as safety and immunogenistic cross protective data become available and warrant its usage.

The industry was given liability relief in the form of the PREP Act earlier this month. And finally, the goal of securing U.S. licensed vaccine product prior to usage was a mandate where possible.

So where are we today with this H5N1 vaccine stockpiling production? We see that we have two clades, clade 1 and clade 2, the clade 1 being the Vietnam strain 1203; the clade 2 being the Indonesian 0505 strain. I draw your attention that a dose for these calculations was based on 90 micrograms per dose and that a vaccine course is two doses per person. In a 2004 campaign, .47 million vaccine courses were produced by Sanofi Pasteur. In subsequent years, in 2005, multiple manufacturers were

producing stockpiles. So in 2005, we had 8 million vaccine courses produced of clade 1 vaccine. In 2006, last year, we had 1 million clade 1 vaccine courses produced and an estimated amount of 4.8 million vaccine courses of clade 2 vaccine.

At this present, we have contracts for at least 1.6 million vaccine courses for this year. And there may be more produced later on in this fall.

So currently, for clade 1 vaccines, we have enough vaccine for 9.5 million persons. And clade 2, we have enough for probably 6.5 million depending on what the actual potency assay data has come out to be. That's an antigen preparation.

Finally, again, why are we here today? Well, one of the things is that today represents the cooperative leveraging of resources throughout HHS, the NIH, CDC, FDA and ASPR with industry to develop, manufacture and test an H5N1 vaccine

candidate most similar to the U.S. licensed seasonal influenza vaccines. Also, today is a discussion of the first H5N1 vaccine candidate that could be licensed for immediate usage if an H5N1 pandemic emerges this year.

Thank you. Any questions? Otherwise, Dr. Linda Lambert from the NIH will share with you the important work that they've done on development of this vaccine.

DR. LAMBERT: Thank you so very much. I've been asked to give you a brief introduction to NIAID's pandemic vaccine research development efforts and then really to set the stage for Dr. John Treanor who will present results from the New England Journal of Medicine article and comment on safety data from some of our follow on studies.

The overall goal of the National Institutes of Health and the National Institute of Allergy and Infectious Diseases

in particular is to serve the public health by conducting and supporting research on infectious and allergic diseases. And as you've heard Dr. Robinson previously indicate, we are all part of a broader Department of Health and Human Services pandemic influenza research plan.

For NIAID, that means research on controlling, preventing and treating seasonal and pandemic influenza. And at NIAID, we do that through a variety of different levels of research from assessing the basic biology of the virus to understanding the immunology and host response to characterize newly emerging influenza strains and understanding the molecular basis of virulence and transmission and to develop and clinically evaluate new diagnostics, drugs and vaccines and to coordinate and collaborate these efforts with other parts of the U.S. Government, most notably DHHS, NVPO, FDA,

CDC and other public health service efforts, and finally, to generate information that will further inform ongoing global pandemic preparedness efforts.

So let me take you back in time. This map looks a little different from some of those that you are familiar seeing with. This is actually the map that is from late January 2004, and you heard Dr. Robinson allude to the outbreaks that were going on in Hong Kong in 1997. But in this map in January of 2004, we were dealing with yet another level of unprecedented outbreak. And so as of just a little over three years ago, there were outbreaks in humans in two countries and poultry outbreaks in a number of countries. And you know subsequently to this slide and over the last several years, that has expanded greatly. But in early 2004, this is what the map looked like.

So NIAID's response to that, that unprecedented level of outbreaks, both in

human and poultry, was to obtain H5N1 vaccines for manufacturers with licensed products as quickly as possible. And in May of 2004, NIAID awarded a contract on behalf of DHHS to Aventis Pasteur, so Sanofi Pasteur, to produce a pilot scale lot of H5N1 using a scaled down manufacturing process that was as similar as possible to their licensed vaccines. And we asked for two formulations, 30 micrograms and 90 micrograms per mil.

So the goal of this -- there were many goals associated with obtaining this vaccine, certainly to gain experience overcoming both technical and logistical issues, and that was for the U.S. Government as well as the manufacturer, so to demonstrate the use of reverse genetics to generate an H5 vaccine reference virus and obtain select agent exemption from the U.S. Department of Agriculture; to produce reagents -- and this was done largely

between Sanofi Pasteur and the FDA to generate the types of reagents that were needed to assess the potency of the vaccine; to develop assay capacity to be able to measure antibody responses to individuals who received the vaccine. And then, really, of all this set the stage for developing a framework and groundwork by which the companies could move to, if needed, commercial-scale manufacturing.

Other objectives -- clearly, to rapidly implement well-controlled Phase I and Phase II clinical trials; to obtain data on the safety and immunogenicity of the vaccine. And the goal for this was to provide initial data comparing dose ranging immune responses to form the basis of additional clinical trials and to assess multiple populations, so just not in health adults but also in the elderly and pediatric populations, and then support the development and use of an H5N1

hemagglutination HI assay and microneutralization assay and be able to have an infrastructure that supported rapid data analysis data collection.

So specifically now focused on Sanofi Pasteur, in June of 2004, NIAID provided a clade 1 H5N1 reference virus to Sanofi Pasteur, and that virus was an A/Vietnam 1203 2004 strain with a neuraminidase and genetically modified hemagglutinin gene and the remaining six genes from the PR8 virus. In March of 2005, Sanofi Pasteur delivered that vaccine to the NAIAD. In April of 2005, NIAID initiated the first H5N1 vaccine in healthy adults. And as you've heard Dr. Baylor say, that was done at three of our VTEU sites, and the study started in early April but was fully enrolled as of May 20th. And then NAIAD transferred preliminary and safety data sets for that study, 04-063, to Sanofi Pasteur for their BLA submission.

So at that point, I'd like to turn it over to Dr. John Treanor who will give you an update or a summary of the results of the adult study. That's NAIAD 04-063 that was published in the New England Journal and a brief overview of our follow on studies.

DR. TREANOR: Thanks, Linda. What I'm going to talk about then is the evaluation of the Sanofi subvirion vaccine made from the reverse genetically engineered virus, created it at St. Jude and put on the PR8 background that was done in health adults at three of NAIAD's VTEUs, our site at the University of Rochester, the University of Maryland led by a co-investigator, Jim Campbell, and the UCLA led by Ken Zangwill in collaboration with SRI which performed the immunologic assays and EMMES Corporation which did data management and statistical analysis.

Now this slide is an overview of

the study design. You can see here where the vaccine was administered, the red triangles; where safety assessments were done; and where antibody sera were obtained. The study was done in a two stage design. Because this was the first human experience with the vaccine, approximately one-quarter of the subjects were enrolled in Stage 1 and were randomized to receive either placebo or vaccine at 90, 45, 15 or 7.5 micrograms. And in addition to assessing safety by memory aids and medical histories and follow-up visits, these subjects also had laboratory safety done before vaccination and on day seven including clinical chemistries, liver function and renal function tests and blood counts.

Now after assessment of the safety data, including a laboratory values, at day seven, the data were reviewed by a DSMB and based on that analysis, the remaining subjects were enrolled and

randomized to receive vaccine or placebo. Similarly, the safety data seven days after the second dose were reviewed by the DSMB prior to Stage 2 subjects receiving the second dose.

After the day 56 or 28 days passed the second dose, the immunogenicity data were available from the Stage 1 subjects and based on all of the available safety date, the decision in terms of designing the protocols for follow on studies in the elderly as well as in pediatric populations were done. And in the elderly, we chose to look at 90 microgram and 45 microgram doses, and in pediatrics, at the 45 microgram dose. Subsequently, these subjects also received a booster dose at day 180 of the same vaccine that they had received initially.

Now in today's presentation, we're going to focus on what was published which is the safety and immunogenicity data

that was available at day 56, that is 28 days after the second dose. Now this is what was published in the New England Journal. It includes all the safety data and immunogenicity data that had been collected up to 28 days after the second dose of vaccine. Just to remind you, the study was done in healthy adults aged 18 to 64 inclusive. It was a prospective, multicenter center, randomized and double blind clinical trial, and the interventions were two intramuscular doses separated by 28 days of either vaccine at 7.5, 15, 45 or 90 micrograms or placebo, and there were 50 placebo recipients and approximately 100 vaccine recipients in each group. The end points that were assessed for safety included both solicited and unsolicited AEs on memory aids and medical history that were done at follow-up visits, and as I mentioned in Stage 1, clinical laboratory tests, and two co-primary immunogenicity endpoints, the

development of neutralizing antibody assessed in NDCK cells using a microneutralization technique and the development of hemagglutination inhibition antibody assessed using horse red blood cells, and both of these assays used the vaccine virus that are reversed genetically engineered virus on the PR8 background as to test antigen.

Now as a handy way of comparing the responses between doses which was the primary goal of this study, we dichotomized the results based on the proportion of subjects who achieved a titer of 1 to 40 or greater in these assays. And that 1 to 40 titer was chosen based on the experience with the neutralization assay in doing sero-epidemiologic studies in the 1997 Hong Kong outbreak as well as our expectations of what background levels of antibody might be in a population in the U.S. and historical experience with HAI data in assessing

protection due to conventional influenza in the inter-pandemic period.

And so this was sort of a composite, but it's important to understand that this choice of a 1 to 40 endpoint is not validated in any way as an actual assessment of protection against H5 in humans. And in fact, it might be just as valid to choose a 1 to 20 or a 1 to 80 or a 1 to 10 endpoint. But it's really more as a convenient way in order to discriminate responses between groups.

Now this is the demographics of the enrolled subjects just to point out that there were approximately 100 subjects enrolled in each of the active dose groups groups and half as many subjects enrolled in the placebo group. The study population is predominantly Caucasian. About half the subjects are female. About 40 percent of the subjects had reported receiving conventional trivalent inactivated vaccine

in the year prior to the study, and the age range was between 18 and 64 with a median just slightly less than 40 years of age.

Now as far as safety is concerned, the vaccine was well-tolerated at all doses that were tested. There was very clearly an increased rate of local pain and tenderness with the higher doses which was different from placebo. Those complaints of pain and tenderness were almost exclusively mild. There were no severe complaints of pain and tenderness. And this gives the results at the 90 microgram dose -- zero complaints of severe, 7 percent complaints of moderate pain or tenderness, and 53 percent of the subjects complaining of mild pain or tenderness at the injection site. I haven't shown the data, but the responses to dose two were almost identical.

There were no differences between any dose group and placebo in the rates of systemic side effects such as myalgias or

fatigue or headache and there were no individuals who developed fever after either dose of vaccine. There was one serious adverse event which was a death which was not judged by the investigators or by the DSMB to be related to the vaccine which occurred within 56 days of dose one.

Now this is a representation of the neutralizing antibody on day 56, that is 28 days after the second dose of vaccine. It shows the reverse cumulative distribution of neutralizing antibody in each dose group. You can see here that the way this chart works is it chose the percentage of subjects in each dose group who achieved the indicated titer or greater so that you can see that as you increase the dose, there is clearly a more vigorous neutralizing antibody response. Using the 1 to 40 criteria that we had chosen, you can see that individuals who received the 90 microgram dose, which is shown in red,

achieved a titer of 1 to 40 or greater 54 percent of the time with 95 percent confidence limits of 43 percent to 64 percent. You can see that the relative superiority of the 90 microgram dose holds true no matter what cut point of titer you chose to analyze. It's also true the 90 microgram recipients achieved a titer of 1 to 20 more frequently and achieved a titer of 1 to 80 more frequently compared to the other dose groups.

Very similar results are seen when the sera are assessed using the HAI assay with horse red blood cells. Again, you can see that 58 percent of the subjects achieved a title of 1 to 40 with 95 percent confidence limits of 47 to 67 percent. Again, there is a very clear dose response relationship in the immune response with subjects who received a 90 microgram dose of showing more vigorous and higher titered antibody responses than those who received

lower doses.

Now as you know, after the study was published in March 2006, there were further discussions with FDA and based on a guidance document which was published in March and further discussions with the agency in April and later in 2006, there was a recommendation for a change in the analysis of the data. And the two changes are that the hemagglutination inhibition test became the primary focus of the immunogenicity analysis based on increased confidence of the accuracy of the HAI test using horse red blood cells, which was a relatively new development and a recommendation that we redefine the value assigned for the first dilution that was tested from 1 to 20 to 1 to 10. An HAI sera response was then redefined with consultation as requiring both a fourfold increase over baseline and achieving a titer of 1 to 40 or greater, again, redefining the

titers as calling the first dilution tested 1 to 10 rather than 1 to 20.

It's important to note that this re-analysis involves recalculations using the 1 to 10 definition of the starting dilution but does not involve any retesting of the sera. It's simply a recalculation. And to show you what this does, this is the data as published. It's a reverse cumulative distribution curve of the HAI data 28 days after dose two. And you can see that the first dilution tested is defined as 1 to 20 so that subjects that showed no HAI activity at the first dilution are assigned a value of 1 to 10 or less. That is why 100 percent of the subjects have a value of at least 1 to 10 or less.

If we redefine the starting dilution as 1 to 10, you can see that this does not change the shape of the curve but does change the values assigned to the x axis. And if we use a criteria of achieving

a titer of 1 to 40 or greater, this changes that estimate to 44 percent with 95 percent confidence limits between 34 and 55 percent. So just to show you, this does not change any of the data but simply changes the way the x axis is defined and the calculation of whether we're looking at this point or this point for dichotomizing the results.

Now as you know, there have been further studies of the Sanofi vaccine. This is just an overview of what other experience exists specifically with the 90 microgram dose. The following number of subjects have received the 90 microgram dose in randomized trials which have included doses of 1, a second dose a third dose. These are the numbers -- the subjects who have received 1, 2 or 3 doses of 90 micrograms.

In addition, there have been open label studies, one of which was a study looking at revaccination of people who had been in a prior H5 study back in '1998.

That involves 37 subjects that we're going to talk about this afternoon. In addition, the vaccine has been given as a 2 times 90 microgram dose to a number of workers involved in making the vaccine at Sanofi as well as laboratory workers at St. Jude's, and you can see the total numbers of subjects who have received vaccines in those open label studies. There have been 363 individuals who received at least 1 dose of 90 micrograms, 304 who have received 2 doses and 166 individuals who have received a third dose of vaccine.

Now in the open label studies, which include the use of the vaccine in manufacturing workers as well as laboratory workers, there have been no serious adverse events related to the vaccine to date, and the rates of local and systemic solicited adverse events are very similar to what had been seen in the control trial at 90 micrograms in health adults in Protocol 04-

063.

The controlled evaluation in the elderly is not finished yet, and so the database has not been locked. There have been 259 elderly subjects enrolled in that study and randomized to receive either 90 or 45 micrograms or a placebo at a 2 to 2 to 1 or a 2 to 2 to 1 ration.

In addition, I'll mention that a subsequent study has also been done in children 2 to 9 years of age. This study only evaluates the 45 microgram dose. Neither database is locked and so only aggregate analysis is available, but no vaccine related serious adverse events have been reported. The local and system reactogenicity has mostly been reported as mild or moderate and appears to be very consistent with the observations in the study in adults.

So with that, I'll end. I'd be happy to answer any questions, or we could

do questions at the end. Okay.

DR. JAMES: Good morning. My name is Andrea James, and I'm a Medical Officer in the Division of Vaccine and Related Product Applications. This morning I'll be presenting the results of the FDA analyses of the immunogenicity and safety data as submitted in the Sanofi Pasteur's H5N1 vaccine BLA.

This slide outlines my discussion points. First, I will give a summary of the product. Following that, I will describe the clinical study supporting this BLA, FUG01, and then discuss the immunogenicity and safety results of the study. I will end my presentation by summarizing the BLA, discussing the limitations of the data and posting the FDA questions to the committee.

The BLA was submitted on October 17, 2006. The product under review is H5N1 influenza virus vaccine A/Vietnam/1203/2004/ Clade 1. The proposed dosage is 90

micrograms, and the proposed administration is 2 one-milliliter IM injections administered 28 days apart.

Sanofi proposes the following indication: H5N1 influenza virus vaccine A/Vietnam/1203/2004/Clade 1, 90 micrographs 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.

FUG01 was the single study submitted in support of this BLA. FUG01 is a Phase I/II randomized, double-blind, two-stage, placebo-controlled, dose ranging study. Subjects were eligible for the study if they were healthy and between the ages of 18 and 64 years with extremes included. Subjects were stratified by age and prior seasonal influenza vaccine receipt and then randomized in a 1:2:2:2:2 fashion to 1 of 5

doses, either saline placebo or 7.5 micrograms, 15 micrograms, 45 micrograms, or 90 micrograms of vaccine. Subjects then received their randomly assigned dose as two intramuscular injections administered 28 days apart.

The study objectives were as follows: One, to determine the dose-related safety of subvirion inactivated H5N1 vaccine in health adults; two, to determine the dose-related immunogenicity of subvirion inactivated H5N1 vaccine in health adults approximately 1 month following receipt of 2 doses of vaccine; and three, to provide information for the selection of the best dose levels for further studies.

In FUG01, the investigators looked at three co-primary immunogenicity endpoints. Two of the endpoints dealt with neutralizing antibody and these data were not submitted to the BLA as per a prior FDA applicant agreement. The BLA submission

included data for the following endpoint analyses: Fourfold rise in HAI antibody titer and HAI antibody greater than or equal to 1 to 40, both measured at 28 days after each dose of vaccine and 6 months after the receipt of the first dose of vaccine.

Of note, the first and last time points are of interest. However, traditionally, HAI titers 28 days post the last dose in a vaccine series is the data usually requested and analyzed in the FDA licensing process.

FUG01 was designed as an exploratory study, so all of the results I'm about to present and to be received with the following information in the forefront of your mind. This study was not statistically powered to provide estimates of immunogenicity at any specific dose. And the study was also not powered to detect rare safety events. Therefore, the results only provide trends.

In terms of subject demographics and baseline characteristics, a total of 452 subjects were enrolled in the study. The majority of subjects were Caucasian female with a mean age of 40.5 years with a range of 18.1 to 64.9 years. The majority of subjects, 58.4 percent had not received the 2004-2005 seasonal influenza vaccine. And interestingly, 3.3 percent of all subjects had detectable H5 antibody at baseline.

Now to go on to the immunogenicity results. On the slide we're looking is a tabular presentation of the first endpoint of percent of subjects who achieved a fourfold rise in HAI titer. In a moment, I will show this data in graph form. However, you can see in this table that the 90 microgram group with 91 subjects in the per protocol population had approximately a 23 percent response rate 28 days after the first vaccination, and a 95 percent confidence interval ranges from 14.9 to

33.1, and a 45 percent response rate 28 days after the second vaccination with a 95 percent confidence interval ranging 34.6 to 55.8 with waning of this response by six months post vaccination two.

This is a graphical presentation of what you just saw on the table. I'll take a moment to orient you to the slide. On the x axis, we have time in days, and on the y axis, we have percent of responders. The blue diamonds represent the placebo arm while the red squares represent the to be licensed 90 microgram dose group with their respective 95 percent confidence interval bars in their respective colors.

There are four distinct time points plotted for each of the study arms: baseline; 28 days after receipt of the first vaccination; 28 days after receipt of the second vaccination; and 6 months after the receipt of the second vaccination. Please note that the dose groups are slightly

separated in time on the graph but that the separation is for graph clarity only.

All subjects were evaluated at the same study time points. This purple hatch mark represents the 40 percent response rate threshold that the FDA currently recommends in the draft guidance document on clinical data needed to support the licensure of pandemic influenza vaccines. It is important to note that neither Sanofi, the BLA applicant, nor NIH, the IND sponsors, were privy to the recommendations held within this guidance, because this guidance was not available until March of 2006, which was nearly a year after FUG01 was conducted.

You can see in this graph that the 90 microgram group is trending, at least the lower bound of the 95 percent confidence interval, is trending towards meeting the criteria, the 40 percent response rate criteria 28 days after the second

vaccination. However, it falls shy of the lower bound threshold by about 5 percent which may be at least partially due to a small study sample size.

This is a graphical presentation of what you just -- actually, this is a dose response graph which I'm putting up to show two things: one, that at all of the vaccine doses tested, there is a dose response as you can see here. And then the second thing that I want to show is as you increase the vaccine dose, you see a dose-dependent increase in fourfold titer rise. So there does appear to be a dose-dependent response.

On this slide we're looking now at a tabular presentation of the second endpoint of proportion of subjects who achieved an HAI titer greater than or equal to 1 to 40. In a moment, I'll show this data in graph form. The numbers are very similar to the numbers that you saw for the fourfold rise. You can see in this table

that the 90 microgram group had approximately a 24 percent response rate at 28 days after the first vaccination and a 46 percent response rate 28 days after the second vaccination. And again, we see waning at 6 months post vaccination 1.

This graph is very similar to the one I just showed you for fourfold rise. Again, in orienting you to the graph, we have time and days on the x axis and percent responders on the y axis. Once again, placebo is represented by the blue diamonds and the 90 microgram group is represented by the red squares with the respective 95 percent confidence interval bars in their respective colors. Once again, the four time points are graphed here, and we have baseline; we 28 days post vaccination 1; we have 28 days post vaccination 2; and we have 6 months post vaccination 2.

Once again, the points are separated in time slightly on the graph just

for graph clarity. Up here you'll see this purple hatch mark, once again at the 70 percent mark. And this, again, is the FDA recommended or requested threshold for HAI titer greater than or equal to 1 to 40. And once again, this is recommended as of March 2006 in the draft guidance.

Once again, you can see that at the to be licensed dose 90 microgram, this group is trending upward. However, it falls well short of the 70 percent threshold that FDA is now currently recommending.

In addition, to the pre-specified endpoint analyses, I performed additional analyses of the following subgroups: gender, race and ethnicity, and the pre-specified strata of age and prior influenza vaccine. Of course, the ends are small but if you look at this per protocol gender subgroup analysis of the 90 microgram dose, you will see that 56 percent of females had a fourfold in HAI titer compared to just 46

percent of males in the study.

Moving on to race and ethnicity. Here the ends for most of the groups are even smaller. You can see that in the race groups, the percent of responders in terms of fourfold increase in HAI titer were fairly equal across the different races. However, if you look at ethnicity, Hispanics appear to respond at a higher rate.

In this slide, I'm presenting the pre-specified strata of age and prior seasonal influenza vaccine, and if you -- the thing, I guess, that jumps out very quickly at you is that the younger group, less than 40-year-old subjects who had not previously had the 2004-2005 influenza vaccine appear to have a higher response rate in terms of fourfold rise in HIA titer. And this is as compared to their counterpart who did receive prior vaccination. So you're looking at a 75 percent response rate versus a 37.5 response rate, again, noting

that the ends are very small.

However, if you look at the group who is 40 or greater in age, you see pretty much the exact opposite where this group did much better, if they received the prior seasonal influenza vaccine versus not having received the prior influenza vaccine; and again, I must stress that the ends are small here and that this is a subgroup analysis.

So in summary, the immunogenicity results suggest that this H5N1 vaccine appears to have a dose-related immune response. And of all the doses studied, the highest dose, 90 micrograms, appears to have a higher response rate with approximately 45 percent of subjects responding after two doses of vaccine. However, immunogenicity observed in the study is less than what is usually seen in seasonal influenza vaccine studies, and the impact of gender, ethnicity and prior seasonal vaccination on H5 immunogenicity is unclear and may warrant

further exploration.

On to the safety results. Safety was assessed by frequency and incidence of immediate reactions occurring 15 to 30 minutes post vaccination, solicited local injection site and systemic reactions measured a day 0 through day 7 vaccination and unsolicited AEs and SAEs measured at day 0 through day 56 of the study. Solicited injection site AEs included pain, tenderness, redness and swelling, and solicited systemic AEs included feverishness, malaise, body aches exclusive of the injection site, nausea and headache.

There were four SAEs in the study, none of which were considered vaccine-related. There was one death in the 45 microgram arm, and this subject was a 52-year-old male with a history of chronic alcoholism, and his death was considered secondary to sequelae of his chronic alcoholism. There were three other SAEs, a

breast cancer in the placebo arm, menorrhagia in the 15 microgram arm, and a cerebrovascular accident in the 90 microgram arm; again, none of these considered vaccine related.

If we look at local reactogenicity events, there appears to be a dose-dependent increase in the frequency of injection site reactions with the 90 microgram group having the most with approximately 85 percent of subjects experiencing at least 1 injection site reaction. The majority of these injection site reactions in this group were pain and tenderness and approximately 14 percent of subjects had injection site reactions that were considered of moderate intensity.

When we look at systemic events, we see that overall they were a lot less common than injection site reactions and that system events did not appear to be dose related. In looking at the specific AEs,

you see that the most common in the 90 microgram group was headache at 38 percent and malaise at about 30 percent. However, the rates for a systemic injection -- or systemic events were similar across all dose arms.

So in summary, the safety results suggest that there is a dose-dependent increase in frequency of local reactogenicity events with the majority of events being pain and tenderness occurring in the 90 microgram group. And these data reveal no other apparent safety signals.

So to summarize, Sanofi has submitted an application seeking licensure for their biologic product, H5N1 Influenza Virus Vaccine A/Vietnam/1203/2004 (clade 1) at a recommended dose of 90 micrograms to be administered as two 1- milliliter intramuscular injections 28 days apart. Based on the data submitted with the BLA, it appears as though the two 90 microgram doses

provide a higher immune response. However, the immunogenicity observed in study FUG01 is less than what is usually seen in seasonal vaccine studies with approximately 45 percent of subjects responding after two doses of vaccine.

Again, there are no apparent safety issues. Unfortunately, there are many limitations of these data contained in the BLA. Therefore, our ability to make firm conclusions about the data are limited. First, the clinical database is small, and as such, is not statistically powered to detect rare adverse events and is not statistically powered to produce statistically significant results. And in fact, these results can only provide trends.

Additionally, the clinical efficacy of this vaccine is unknown. A correlative protection against H5 is unknown. And the impact of gender, ethnicity and prior seasonal influenza

vaccination on the immune response to this H5N1 vaccine is unknown.

With that, I will move on to give you a brief look at the questions to the committee reminding you that Sanofi's proposed indication is that their vaccine will be indicated for active immunization against influenza disease caused by H5N1 A/Vietnam/1203/2004 (clade 1) influenza virus and that primary vaccination of healthy adults 18 through 64 years of age --

The questions we will be discussing later on today and presenting to the committee are: Are the data sufficient to support the effectiveness of this product for use during a pandemic or in situations of potential high risk exposure; 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 lastly, please comment on studies to collect additional information about the

effectiveness and safety following this vaccine's use. The questions will be presented again later on, prior to our discussion.

Before I end, I'd just like to acknowledge all of the people who helped me in developing this presentation. I specifically would like to give great thanks to Dr. Tammy Massey, Dr. Zhiping Ye, Dr. Melissa Baylor, Dr. Antonia Gerber and Dr. Joe Toerner whose time and resources and knowledge and expertise made this presentation possible. Thank you.

DR. KARRON: Thank you, Dr. James. At this point, we'll take questions for Dr. James or for any of the previous presenters. Dr. Couch?

DR. COUCH: Most of my questions are procedural. I guess I'm directing them to Dr. Baylor maybe. But I need a little -- maybe some of the other committee members -- a little better understanding of the role of

the FDA and maybe of this committee in licensing a vaccine like this. You know, we've said and many of us have earlier understood that this would represent a strain change. You see? And yet we're considering a licensing application because we wouldn't license the strains we're about to select for next year. But on the other hand, if we license H5, do we also have to license H7, H2 if those come down the line? And where do we stand with regard to considering individual vaccines that are using, as you pointed out, a pre-existing approved procedure for preparation?

DR. BAYLOR: I can start out answering that, Bob. I mean, you know, this is sort of new ground here. And the -- the procedure is basically -- I mean for this vaccine it's -- we're saying it's manufactured by the same process as the currently licensed vaccine. And so in some sense it's a strain change, but you have to

keep in mind that we at least need some dose ranging studies. So we need to figure out what the dose is for this vaccine and, therefore, we have a clinical study which has, you know, gone down that road to try to do that. And so we're -- also, this vaccine will be labeled with a different name to differentiate it from the current seasonal vaccine, so we're calling this an application.

Now if we -- let's start with something like a new clade. Well, how would we handle a new clade? So it's a H5. That's more like a strain change supplement, like, for instance, tomorrow when you decide on what the strains will be for next season's vaccine. However, for the H5, since we have very little experience with that, we may require clinical data for the next clade. And in fact, we know that some studies are being done with the H5N1, Indonesia. So that would be -- that would

come in with additional more supportive clinical data as far as looking at the dose, because we -- we just wouldn't be able to predict that.

Now if you move into NH7 or that H7, if it was manufactured by a licensed procedure, it would follow the same process. But we still would need some kind of -- and again, same process in the sense that we would need some kind of supportive clinical data to, at a minimum, determine the clinical -- the dose required. And so I think that sort of addresses your question how we would do that.

DR. COUCH: Yes. I think it does, but I think you would agree then in the process of doing this, then we're not literally looking at a brand new vaccine proposal. For example, with regard to something like this, you see, this is an established procedure and the H5 has made itself into a green monster disease wise,

but I don't think the virus knows that. And we've changed the hemagglutinin up on the top. You see? So there's an absolutely safety data for this procedure and for other vaccines that ought to be, I would say, considered from that point of view.

Now from the point of view of looking at the dose and things like that you see, you can see individual considerations for each one that comes forward. But it would -- we would not want it to be considered a brand new virus starting from scratch to look at everything. I guess that was part of my question.

DR. BAYLOR: And you're correct and we agree. I mean you -- we're not saying we're going to bring -- every time we do this, we're going to bring one to you. But I mean this is the first and so we believe it's really important to have this discussion, have you look at the data, although the data are limited. But this is

-- and I don't think we should get sort of wrapped up in what we call this thing as far as the submission. I mean it's not a brand new product as for example we came in and changed the manufacturing process completely or we had an adjuvanted vaccine. That would be brand new product. But -- so what we're -- what I'm saying is this is -- don't get confused by what we're calling this. You know, this is a first of its kind and we're bringing it to you with the limited data for the reasons that we explained earlier.

DR. COUCH: This one is just -- one more and I'll quit -- minor. And then with an licensed approval for this, does that -- what kind of freedom does Sanofi have with that? I mean, for example, most of us would say if we could hang a shingle out on the streets that we have a bird flu vaccine for sale, we'd get rich in a big hurry. Now that would be politically unwise for them, but what sort of freedom does this

give them?

DR. BAYLOR: Well, I can let Sanofi respond to this, but I mean we all presented in our slides, or I did and I believe Sanofi did as well, this vaccine will not be commercialized. It will be for the stockpile, and Dr. Robinson has stated that as well.

DR. COUCH: The license will be for the stockpile, specified that way?

DR. BAYLOR: Well, that's a little -- that's -- you know, we have to make those decisions, but this vaccine -- if we license this vaccine, it will be licensed, but it will be licensed for what it is.

DR. KARRON: Dr. Webster?

DR. WEBSTER: We've heard that this is not a new vaccine, but indeed, it is a new vaccine being made by totally new strategies, by reverse genetics, and this is really a very historical event when we're

faced with the use of reverse genetics virus to make a vaccine and then provide that vaccine to humans.

And it's a genetically modified organism that you're talking about putting in human. This was mentioned in passing, stress where we made issues that come from the use of a reverse genetics. I can get past, is this the reason for the poor immunogenicity in this thing? Is this why it produces that poor amount of hemagglutinin? These are all scientific messages that are out that, but my point is that this is a whole new strategy we're using to make this vaccine. And we have to have that on the table as we think about it.

I think that the use of such a vaccine is the roadmap to the future. We've been using reverse genetics within the States over many years. And now we make these viruses by reverse genetics exactly as we need them, and this procedure has shown

that these vaccines are genetically tainted. The question that was raised earlier is if you use reverse genetic process on this highly pathogenic virus, will it be safe for manufacture, will the manufacturers be safe. And I think that these are issues that every worker in immunogenicity, I would have nothing to do with this vaccine. I will conclude - I don't know whether it's necessary, but I just wanted say that.

DR. KARRON: Dr. McInnes.

DR. McINNES: Rob, I want to clarify one thing. I want to be sure that you did not state that genetically modified organism is being put into people. At one point, that was where I thought you were heading, and I want you to please clarify that.

DR. WEBSTER: (Inoperative microphone)

MS. WALSH: Excuse me. May I interrupt? I'm sorry. I was just told that

your microphone is not working, so if you could use Dr. McInnes'? Thank you very much. We appreciate that.

DR. WEBSTER: The light was working. Sorry about that. The genetically modified aspects of this organism, yes, a genetically modified organism was made. It was inactivated and made into vaccine which we've heard this morning, so it was a genetically modified organism that we began with.

DR. KARRON: Dr. Modlin?

DR. MODLIN: I have a couple of unrelated questions. I guess the first is for Sanofi, and that is what are the plans for extending the age range for approval for this vaccine to children and to the elderly? Obviously, we have studies under way, but I'd be real curious as to what the thinking is with respect to the timeline for bringing forward what I assume would be a supplement.

MR. GUITO: So keeping in mind

that the discussions around this license application started roughly a year ago, the data that was available at that time was the data in 18 to 64 year olds. There were subsequent trials done with the NIH in the pediatric population and in the elderly population. That data has only recently become available. Dr. Treanor and Dr. Lambert are ready to discuss that data today. I think when we reach conclusion on this issue with the 18 to 64 year old indication with the FDA, we will then initiate discussions about broadening that population.

DR. MODLIN: Maybe I could ask Bruce Gelling or some of the others that have been actively involved in these discussions what might happen in terms of use of this vaccine if it were stockpiled and we have a -- we're faced with a clade 2 epidemic?

DR. GELLIN: Well, I mean we

started the process -- I think in Robin's slide -- you may want to address some of this -- in 2004, and the goal was to have vaccines in the stockpile that would be relevant to what was circulating at the time and this has begun to move forward. We don't know whether or not a vaccine like this would provide some, any, much protection and I think the idea is that since it could provide some, I think the concept is that in the setting with an imminent pandemic, you would begin to use what you had available.

There will be discussions later today in the second session about how other -- how vaccines might be used more in a different way and regarding immunologic priming. But I think that right now the idea is that you'd use the vaccine that you had and hope that it provides some protection. And this is the sort of a stopgap as you begin to make the vaccine

against the pandemic.

DR. MODLIN: But that would be the case even though the label would say this is indicated for use in the event of a clade 1 epidemic?

DR. GELLIN: I guess there is the -- you know, given that labeling, I guess I'll ask others to respond to that, because, again, we don't know. We do know that with other vaccines when there is a mismatch, there is some protection. So I think that the idea would be that you could get some but not perfect protection, but maybe FDA would like to respond to that.

DR. KARRON: Dr. Couch?

DR. COUCH: Perhaps. I just wanted to add a comment sometime -- this may be appropriate -- that we don't really know, as Dr. James said, what is required to predict against an H5 pandemic strain any more than we'd know about H7. And so when we're looking at the criteria that she

showed us, those, our European colleagues have perpetuated those fairly extensively, but we haven't used them much in this country. But those are frames of references that way I think of them when you're talking about H5, for what kind of immune responses you're getting, they cannot be used, I think most of us agree, as a criteria for an approval based on some idea about protection. We just simply don't know what we need, and I'm one of the views that anything is better than nothing which then relates a little bit to Bruce's question, and that should be what we have in mind when we decide to approve a vaccine, not where how close it came to the lines that Dr. James showed us.

DR. KARRON: Dr. Jackson and then Dr. Farley.

DR. JACKSON: Well, Dr. James presented some information on fourfold response by age and prior vaccine

stratification, and those data, while limited, suggest potentially important interactions in vaccine response by age and possibly by prior receipt of seasonal influenza vaccine. And so it seems relevant to know more about that. While the study was conducted among persons 18 to 64, that does not necessarily mean that there was homogeneity of response or dose response across that entire age range.

So I wondered if there was additional information available on one, the distribution of age among the groups less than 40 or greater than/equal to 40, specifically interested in the proportion of individuals in the higher end of that age range; if there is information on the RDC curves to give estimates of both effective age as well as whether dose response actually varies by age; and then whether safety data has been evaluated by strategies of age and/or prior vaccine response?

DR. JAMES: In terms of your first question, what I've looked at were the stratification, so as I presented the stratification of age and prior influenza vaccine, I do not have currently have information on those particular strata. But I did look at safety data based on gender and based on age, and there -- again, the data are limited. There are no apparent signals with those.

Can you repeat -- you asked me another question on --

DR. JACKSON: Yes. Thank you. You presented the fourfold rise data. I wondered if the response to achieving a titer of 1 to 40 are greater, specifically the RDC curves, if there were any information on the relationship of age and possibly vaccine receipt on those other measures of the vaccine response and dose response?

DR. JAMES: Okay. In terms of

the stratification, I did look at -- I didn't look at all of the doses, but I did look at the 45 microgram dose for the stratified groups and the results were similar to what was shown for the 90 microgram group. I didn't look at the 15 or the 7.5 microgram group. And I need to answer another question for you I think.

DR. JACKSON: No. I think that's it. Just an interpretation of the data, I mean the data are consistent although not -- they do not prove that the dose response and the evidence for some response are actually restricted to a particular subgroup which is the less than 40 with no prior vaccine receipt, and I think that's important considering the implications for the overall results.

DR. KARRON: Dr. Farley?

DR. FARLEY: Well, I guess I'm struggling a little bit with the guidance that has now been published which was after

the fact, so the March 2006 guideline, they're not binding but suggestions for parameters of immunogenicity. And while I understand we're in a situation of wanting to be ready in responding, how will this impact -- I mean, those in general, that wasn't met, the guidance was not met with this vaccine in terms of immunogenicity which may be okay if it's better than nothing, you know, in an urgent situation. But will we -- will this be modified over time? Are we going to expect more with each additional or each further refinement of these vaccines as they go along?

Or, you know, it's a struggle here to say it didn't really meet -- it isn't all that immunogenic if we are -- if this reflects anything close to correlates of protection and we don't know that. But I guess I'm struggling between urgency and needing to have something available versus sort of where -- how low to set the bar for

immunogenicity.

DR. KARRON: Dr. Goodman?

DR. GOODMAN: Well, I was going to comment anyhow and follow-up on what Dr. Couch said which is, I think, relevant. And he might want to comment. These guidances, just like the European criteria, are set as, in this case, as a goal, as this is something that would be desirable. As Bob Webster said, this H5 is poorly immunogenic. Also, as Dr. Couch said, and he's written extensively about it, what you see with these levels of hemagglutinating antibody is basically the higher the levels are, they correlate in a population with more protection.

However, that does not mean at levels lower than this, in many circumstance, there is not substantial protection. So there's no a perfect correlate mapped out. We know at least from seasonal influenza that levels lower than 1 to 40 can have a protective

affect, and as Norman mentioned, and I'll mention later this afternoon, some of this in modeling also plays out as showing a beneficial affect.

So I think the guidance was intended to set goals. The better an antibody responds, the better. We're all hopeful that new technologies will achieve a better antibody response with this antigen. But right now, in terms of a vaccine with a safety profile that is well-established and could be acceptable in broad use this is where we're at.

DR. KARRON: Actually, just a comment that I wanted to make in response to that, and I'd ask other influenza experts around the table to comment, you did say, Jesse, that in general, higher titers of antibody correlate with increased protection. That's true, we think, for seasonal influenza. I don't think we have those data for pandemic influenza, and if

anyone wants to correct me, please do.

DR. GOODMAN: Yes. Well, I think we should go around and ask people, but I think we -- there are not a lot of reasons to think that, you know, pandemic may be more like in children, for example, where you don't have a history of chronic exposure to other antigens. But I think all we can say is that we know from in annual influenza, that there's a correlate. And you're correct, we don't know with pandemic that there is or exactly what it is or that the curve would follow the same level.

DR. COUCH: I think we know --

DR. GOODMAN: There's reason --

DR. COUCH: -- in a general sense.

DR. GOODMAN: Well, I was going to say there's no reason to think not.

DR. COUCH: Well, actually, in 1957 says that indeed, if you've got a vaccine response to that antibody -- Ted can

comment on this -- you were protected. Now, can you -- is there nice quantitative, correlated data with all of these titers like we tend to look at now? I can't remember any if there was. But it was pretty clear that a vaccine response induced protection. It was actually less clear in '68, but it was also there. So I think we can still use that generality even if we can't take a titer and put numbers and percentages on. Ted, you may want to comment on that.

DR. EICKHOFF: Yes, I agree, but the amount of H2 vaccine produced in 1957 was really very limited, and so those studies are very limited. However, certainly for seasonal flu, it's been amply confirmed time after time after time that higher HAI levels correlate with protection

If I may, may I ask another question? Two questions as a matter of fact. First one to either Dr. Treanor or

Dr. James. I'm interested in the thinking that led to the recalculation of the results. What was accomplished here? You set the bar higher, obviously, made it a more stringent test. What was the thinking that led to this?

DR. COUCH: Could I comment on that because I understand. It was a very simple error as I understand. Well, maybe I shouldn't call it an error, just doing things in a different way.

DR. BAYLOR: It was -- I mean what we used was normal convention, and I think that the purpose -- you know, NIH was -- and NIH and John can speak as well -- but they were looking at microneuts. and HAI and so it was a different purpose in how they were calculating -- how they -- the convention they were using for the assays. But we used what was normally considered the standard convention. And so, I mean, there's no magic here or any -- you know, I

don't want to dwell on it.

DR. EICKHOFF: I understand. Second question -- perhaps Bruce might comment on this -- but what would be the trigger for a use of this product?

DR. KARRON: Actually, before that --

DR. TREANOR: Just so people are clear about the difference between 1 to 10 and 1 to 20, the way these tests are done is that the sera is diluted to 1 to 10, that's 2.5 microliters of serum in a volume of 25 microliters of buffer or RDE. So that's a 1 to 10 solution. Then serial dilutions of that are made. An equal volume of virus is then added, and that is the reaction in which antibody and virus interact. So depending on your philosophy, you could call this a 1 to 20 dilution or you could call it a 1 to 10. There would be a valid argument for either. The laboratory that did the testing by convention called this a 1 to 20

dilution. But there are many other labs which would call it 1 to 10. I think there was an effort to try to harmonize the definition with what other people used that led to the reclassification. But this is essentially what we're talking about here.

DR. EICKHOFF: Thank you.

DR. TREANOR: Right. And the other important point is everything started with the microneutralization test, and that's where this definition came from. And then we wanted -- the HAIs would use the same definition so it wouldn't appear that one test was artificially more sensitive than the other. So for our studies, everything used this convention as calling what the starting dilution was. When you go back to using HAI, it's more conventional to use this definition. And that's sort of how things evolved as HAI became more important than neutralization.

DR. EICKHOFF: Thank you. Second

question for anybody and perhaps Bruce. What would be the trigger for use of this quote pre-pandemic vaccine?

DR. GELLIN: So, again, the terminology gets tangled. This is a pre-pandemic vaccine. We're not talking about a pre-pandemic vaccination program. So those often get confused. So the idea is that this is what you'd have available with the declaration of a pandemic as you then were going back and creating the pandemic vaccine.

DR. KARRON: Actually, Bonnie, did you have a comment?

DR. WORD: I just had a question that part of it is following up what Dr. Modlin had mentioned when he asked about other groups. He asked about children and elderly. I guess my question was related to what plans did Sanofi have for looking at high-risk groups? Because when you start looking at that one slide when you talk

about the difference in ages and how they responded, perhaps, as Dr. Jackson mentioned, most of your high-risk individuals fall into that greater than 50 age group? And I don't know if they're planning on looking at that group, because that would be the majority of people. That's why we chose that age -- or that age was selected.

MR. GUITO: So as I mentioned earlier, Sanofi Pasteur has extensive development efforts underway looking at not only traditional manufacturing methods but some novel approaches with cell-based production and different adjuvant approaches as do many other manufacturers. And we think that our direction is best served in this area rather than expand the studies with the 90 microgram formulation at this point.

DR. WORD: So the answer is no, you're not going to look at it in high-risk

groups?

MR. GUITO: The answer is no.

DR. KARRON: Dr. Self.

DR. SELF: So I'd like to go back a little bit to the use of this. There's a question about the trigger but trigger for what? The -- I mean there's this prospect of pandemic which raises all sorts of images and where I'm being asked to make some balance between the risks and benefits of this vaccine. While anything is better than nothing in a general sense, there is a specific use in mind. And so there does seem to be some sort of minimum level of efficacy that we need to be thinking about in making this balance. So could you describe a little more what this -- how this stockpile would be used and what the modeling that was briefly alluded to suggests as a minimum level of efficacy that would have enough merit to warrant the investment and licensure?

DR. GELLIN: Only because I'm closer to the mic, but I'm reading off of Dr. Robinson's slides, and I'll ask Norman to address the modeling piece which he had in his, but his first two bullets on Robin's slide 6 were that the goal was to establish a stockpile for 20 million persons and the critical workforce including first responders for use at the onset prior to the release of a well-matched vaccine. So that's the purpose of this stockpile. It's different than other stockpiles for other purposes, and remember it was sized for just a small portion of the population at that -- as the first responders. But -- so you can ask me more about that or I can turn to Norman about the modeling piece.

DR. SELF: Maybe we can hear about the modeling.

DR. KARRON: Well, I think, Dr. Robinson, did you want to comment a bit more on that first and then the modeling?

DR. ROBINSON: Two things. One is that the department and the administration certainly has two goals here, and one is to sustain the constitutional government and to maintain social and economic order at the onset of a pandemic. This vaccine has been set here as a stopgap measure until a well-matched vaccine is available from the vaccine manufacturers after a pandemic declaration. When a pandemic is declared by WHO or independently by the President or the Secretary for Health and Human Services can vary, you know, a little bit. And so if it seemed to be imminent and it's worthwhile to move to declare that pandemic such that we can start moving forward, then that would be done.

Secondly, as far as the modeling studies, and Norman can certainly attest to this, too, is that what's been seen is that if you have a vaccine that has as little as 33 percent match in efficacy for the