FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANTIVIRAL DRUGS ADVISORY COMMITTEE

AND

THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

October 29, 2008

8:00 a.m.

Hilton Washington, DC/Rockville
Rockville, Maryland

C O N T E N T S

C O N T E N T S (Continued)

P A R T I C I P A N T S

Ian McGowan, M.D., Ph.D., FRCP, Chair
Paul Tran, RPh, Designated Federal Official AVDAC

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEMBERS (AVDAC) (Voting)

Ian M. McGowan, M.D., Ph.D., FRCP
Barbara Alexander, M.C.
Janet W. Anderson, Sc.D.
Marshall J. Glesby, M.D., Ph.D.
Peter L. Havens, M.D.
Craig Hendrix, M.D.
Amneris E. Luque, M.D.
Tracy Swan (Patient Representative)

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Joseph S. Camardo, M.D. (Industry Representative)

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

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William H. Shrank, M.D. MSHS
Jan L. Hewett, J.D., BSN

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Terry C. Davis, Ph.D.

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John S. Bradley, M.D.
Eric P. Brass, M.D., Ph.D.
Ruth S. Day, Ph.D.
Marilyn S. Eichner (Patient Representative)
Neil J. Farber, M.D.
Marc Lipsitch, M.D.
Robert P. Mauskapf, MPA
Yoshihiko Murata, M.D., Ph.D.
Richard A. Neill, M.D.
Ruth M. Parker, M.D.
Leslie Walker-Harding, M.D.

REGULAR GOVERNMENT EMPLOYEES (Voting)

Chester (Bernie) Good, M.D., MPH
Alexander Klimov, Ph.D.
Timothy Uyeki, M.D.

FDA PARTICIPANTS (Non-Voting)

Edward M. Cox, M.D., MPH
Andrea Leonard-Segal, M.D.
Linda Lewis, M.D.
Debra B. Birnkrant, M.D.
Scott Proestel, M.D.
CAPT Laura Shay, R.N., M.S., C-ANP

CENTER FOR DRUG EVALUATION AND RESEARCH GUEST SPEAKERS (Non-Voting)

Frederick Hayden, M.D.
John Tegeris, Ph.D.

PROFESSIONAL ASSOCIATIONS GUEST SPEAKERS (Non-Voting)

Henry (Hank) Bernstein, D.O.
Representing: American Academy of Pediatrics(AAP)

James Blumenstock
Representing: Association of State and Territorial Health Officials (ASTHO)

Luciana Borio, M.D.
Representing: Infectious Diseases Society of America (IDSA)

Marcie Bough, Pharm, D.
Representing: American Pharmacists Association (APhA)

Brit Oiulfstad, D.V.M., M.P.A.
Representing: National Association of County and City Health Officials (NACCHO)

Doug Campos-Outcalt, M.D., MPA
Representing: American Academy of Family Physicians (AAFP)

Litjen (L.J.) Tan, M.S., Ph.D.
Representing: American Medical Association (AMA)

Cynthia Reilly, B.S. Pharm
Representing: American Society of Health-System Pharmacists (ASHP)

P R O C E E D I N G S

Call to Order and Introduction of Committee

DR. McGowan: Good morning, everyone. My name is Dr. Ian McGowan and I am the chair of the Antiviral Drugs Advisory Committee. I would now like to call the joint meeting of the Antiviral Drugs Advisory Committee and Nonprescription Drugs Advisory Committee to order.

However, before we begin I would like to ask Dr. Andrea Leonard-Segal, Director of the Division of Nonprescription Clinical Evaluation, to make a special presentation. Dr. Segal will present a plaque to Dr. Ruth Parker for her service on the Nonprescription Drugs Advisory Committee.

DR. LEONARD-SEGAL: Dr. Parker, can you join me up here, please?

On behalf of FDA, it is a pleasure for me to present this plaque to you this morning. We have very much appreciated the wonderful work, and we have learned a tremendous amount from you over the last four years, particularly in the area of healthcare communication.

So, let me just read the plaque which says: U.S. Food and Drug Administration Advisory Committee Service

Award presented to Ruth M. Parker, M.D. in recognition of distinguished service to the people of the United States of America, Nonprescription Drugs Advisory Committee, Center for Drug Evaluation and Research, from January, 2005 to May, 2008. Thank you and congratulations.

DR. PARKER: Thank you. Thanks very much. I will try to behave today.

[Applause]

DR. McGOWAN: The following statements have been approved by the FDA's Office of Chief Counsel: For the topics such as those being discussed at today's meeting there are often a variety of opinions, some of which are quite strongly held.

Our goal today is that the meeting will be a fair and open forum for the discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair, and we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the advisory committee members take care that their

conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. A press conference will be held in Plaza I immediately following the meeting today.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you. I will now pass over to Paul Tran.

DR. TRAN: I would like to make a quick announcement for everyone to, please, silence your cell phone and blackberries or pagers before we start, and I would like to identify the FDA press contact person. Miss Karen Reilly, if you are here, could you please stand up? She is not here yet. We will identify her later on this afternoon. Thank you.

DR. McGOWAN: I think we would now like to go around the table and introduce our very large and augmented committee or committees. I believe, Paul, we will start from the left at the far end. So, perhaps I could ask Dr. Edward Cox to begin with introductions and we will work

around the table.

Introduction of Committee

DR. COX: Good morning. Ed Cox, Office of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debra Birnkrant, Director of the Division of Antiviral Products, CDER, FDA.

DR. LEONARD-SEGAL: Andrea Leonard-Segal, Director of the Division of Nonprescription and Clinical Evaluation, CDER, FDA.

CAPT SHAY: Laura Shay, social science analyst, Division of Nonprescription and Clinical Evaluation.

DR. LEWIS: Linda Lewis, medical team leader, Division of Antivirals, CDER, FDA.

DR. PROESTEL: Scott Proestel, acting medical team leader, CDER, Antivirals, FDA.

DR. GOOD: Chester Bernie Good. I am the Chair of the Medical Advisory Panel for the Department of Veterans Affairs. I am from Pittsburgh.

DR. MURATA: Yoshihiko Murata, University of Rochester Medical Center.

DR. LIPSITCH: Marc Lipsitch, Harvard School of Public Health.

DR. BRADLEY: John Bradley, pediatric infectious diseases, Children's Hospital, San Diego.

MR. MAUSKAPF: Bob Mauskapf, Director of Emergency Operations, Virginia Department of Health.

DR. SHRANK: Will Shrank, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School.

DR. GRIFFIN: Marie Griffin, Department of Preventive Medicine, Vanderbilt University.

MS. SWAN: Tracy Swan, Treatment Action Group, New York City.

DR. ALEXANDER: Barbara Alexander, from Duke University. I am Director of Transplant Infectious Diseases.

DR. ANDERSEN: Janet Andersen, Harvard School of Public Health.

DR. HAVENS: Peter Havens, pediatric infectious diseases, Medical College of Wisconsin, Milwaukee, Wisconsin.

DR. McGOWAN: Ian McGowan, University of Pittsburgh, Pennsylvania.

DR. TRAN: Paul Tran, designated federal official

for the Antivirals Drugs Advisory Committee.

DR. GLESBY: Marshall Glesby, infectious disease specialist, Weill Cornell Medical College, in New York.

DR. HENDRIX: Craig Hendrix, clinical pharmacology, Johns Hopkins.

DR. LUQUE: Amneris Luque, Division of Infectious Diseases, University of Rochester Medical Center.

DR. HEWETT: Jan Hewett, University of Michigan Medical School.

DR. PARKER: Ruth Parker, Department of Medicine, Emory University School of Medicine.

DR. KLIMOV: Alexander or Sasha Klimov, Influenza Division, Centers for Disease Control and Prevention.

DR. UYEKI: Tim Uyeki, Influenza Division, CDC.

DR. DAVIS: Terry Davis. I am in the Department of Medicine at LSU Health Sciences Center in Shreveport. I am a psychologist and I think I am on here because of health literacy.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University.

DR. NEILL: Richard Neill. I am a family physician from the University of Pennsylvania, home of the National

League Champion, Philadelphia Phillies.

MS. EICHNER: Marilyn Eichner, FDA advisory committee.

DR. WALKER-HARDING: Leslie Walker-Harding, Chief of Adolescent Medicine at University of Washington and Seattle Children's.

DR. BENOWITZ: Neal Benowitz, Clinical Pharmacology, University of California, San Francisco.

DR. BRASS: Eric Brass, Harbor UCLA Medical Center, Department of Medicine.

DR. FARBER: Neil Farber, Department of Medicine, UC, San Diego.

DR. CAMARDO: Joe Camardo, Wyeth Pharmaceuticals.

DR. NELSON: Last but, hopefully, not least, Ed Nelson, Vice President of Medical Research, Martek Biosciences.

DR. McGOWAN: Well, thanks very much, everyone, for introducing yourselves. As you can see, we have a busy timetable and a lot of people on the committee so, as we proceed through the day, it is totally worth everyone considering to be focused in terms of their questions and discussion so we can all make a contribution.

First of all, I would now like to pass it over to Dr. Debra Birnkrant, the Director. Oh, yes, I am sorry, before I do that Paul is going to read the conflict of interest statement. Debra, just hang on a minute.

Conflict of Interest Statement

DR. TRAN: Good morning. The Food and Drug Administration is convening today's joint meeting of the Antiviral Drugs and Nonprescription Drugs Advisory Committees under the authority of the Federal Advisory Committee act of 1972. With the exception of the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetics Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committees are in compliance with

federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the Federal Food, Drug and Cosmetics Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential conflict of interest when necessary to afford the committee essential expertise.

Related to discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts/grants/CRADAs, teaching/speaking/writing, patents and royalties, and primary employment.

Today's agenda involves types of studies and trial designs needed for an influenza antiviral MedKit for the

treatment or prophylaxis of pandemic influenza and to discuss publicly the proposed development program that would support an application for such a MedKit. Issues such as the role of personal MedKits, home stockpiling, nonprescription availability of influenza medications and interfaces of home readiness with public health systems will be raised in the course of the discussion.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. John Bradley. Dr. Bradley's waiver is for his employer's subcontract for a federally-funded study. The study is related to a potentially affected product for an unrelated indication. The funding falls between $0 and $50,000.

The waiver allows Dr. Bradley to participate fully in today's deliberations. FDA's reason for issuing the waiver is described in the waiver document, which is posted on FDA's website at www.fda.gov/phrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information

Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting, and will be included as part of the official transcript.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comment made by the speakers.

Dr. Frederick Hayden has acknowledged multiple grants from GlaxoSmithKline and Hoffman LaRoche to his employer, the University or Virginia, prior to 2002. He has not received any consulting or speaking fees since 2005. He is an unpaid member of the oseltamivir-H5 advisory group on preclinical studies to Hoffman LaRoche, which began in 2005. Lastly, he is the past co-chair and current member of Neuraminidase Inhibitor Susceptibility Network , NISN, from 1999 to present. NISN receives financial support from Hoffman LaRoche and GlaxoSmithKline.

Dr. Henry Bernstein has acknowledged that he is a researcher on GlaxoSmithKline immunization trials.

Dr. Marcie Bough has acknowledged that as a non-

profit organization, the American Pharmacists Association receives unrestricted grants from firms for educational programming.

Dr. Doug Campos-Outcalt has acknowledged that he presents two to three talks per year for AFaces of Flu@ which is a speakers bureau out of Rush Medical School.

Dr. Luciana Borio has acknowledged that she is employed as a senior associate members at the Center for Biosecurity at the University of Pittsburgh, in Baltimore, and as an assistant professor of medicine at Johns Hopkins University.

As guest speakers, Drs. Hayden, Bernstein, Bough, Campos-Outcalt and Borio will not participate in committee deliberations, nor will they vote.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Joseph Camardo and Edward Nelson are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Both Dr. Camardo's and Dr. Nelson's role at this meeting is to represent industry in general and not any particular company. Dr. Camardo is an employee of Wyeth. Dr. Nelson is am employee of Martek.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. McGOWAN: Thanks, Paul. Now we will proceed with the opening remarks by Dr. Debra Birnkrant, Director of the Division of Antiviral Products.

Opening Remarks

DR. BIRNKRANT: Thank you and good morning. I would like to welcome everyone to today's joint advisory committee meeting on MedKits for influenza.

I would like to recognize both the Antiviral Products Advisory Committee members and the Nonprescription Products Advisory Committee members, as well as our consultants and speakers. In addition, I would like to recognize representatives of the Department of Health and

Human Services and professional societies. Lastly, I would also like to recognize FDA reviewers who worked diligently on this project.

[Slide]

Today's meeting will focus on antiviral MedKits for home stockpiling for use during a pandemic. Although safety and efficacy data from trials of neuraminidase inhibitors were presented before the antivirals committee for acute, uncomplicated seasonal influenza, today's topic will not include a presentation of new clinical data. That is, today's meeting is both a policy and development meeting where we will be discussing the concept of a MedKit and what additional studies would be needed to ensure safety and efficacy of this new product.

In my comments I will briefly describe how we envision the MedKit process; comment on the background and purpose of this meeting; mention the approved influenza antivirals; discuss considerations for a MedKit and types of studies to enhance communication of important messages related to this new dosage form before reviewing the agenda and questions with you.

[Slide]

What is an influenza MedKit? It is a specially designed package with new labeling containing an approved antiviral drug for prophylaxis and/or treatment of influenza for use during a pandemic. It is currently proposed as a prescription product for home stockpiling.

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We expect that it will be submitted as a supplemental NDA to the existing NDAs for Tamiflu and Relenza because it relies on previous safety and efficacy data that supported the original approvals.

In addition, we will need evaluation of use in the intended population for the new proposed use and to evaluate additional labeling.

We are applying the nonprescription drug development model for means of communication regarding the MedKit because patients will need to decide when and how to use the MedKit. They will have to self-select or determine if they have the condition for which the drug is indicated, and it is likely that use will occur at a time distant from interaction with a healthcare professional.

The supplemental NDA would include additional consumer studies, such as label and comprehension studies

and actual use studies, and CAPT Shay will be providing an overview of these.

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As further background to the concept or the origin of the MedKit, HHS officials expressed their interest in pursuing MedKits as part of their support of personal preparedness for pandemic influenza.

Briefly, HHS asked Roche and Glaxo, or GSK, to propose studies and development plans for a home MedKit for use during a pandemic. HHS then asked FDA if they would work with the sponsors to outline a development pathway. We provided such advice to both companies via face-to-face meetings and/or teleconferences. Further details on HHS's approach to MedKit development will be provided by Dr. Tegeris on BARDA.

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Previous departmental meetings on this topic discussed such issues as the potential effects of MedKits on reducing the impact of a pandemic, equity and affordability. But this is not the purview of FDA. Rather, FDA's responsibility is to assess safety and efficacy of a proposed product for its intended used with the available

instructions, based on review of submitted data. Therefore, we are here today to obtain advice and generate discussion about proposals for influenza antiviral MedKits, to assess risk/benefit regarding the concept of a MedKit, appropriate supportive studies and other issues such as resistance.

[Slide]

Let me briefly cover the approved antivirals for influenza, and this will be covered in other presentations later this morning. There are only four drugs approved for treatment or prophylaxis of influenza. We have the older M2 inhibitors, that is, amantadine and rimantadine, and the newer neuraminidase inhibitors. Widespread resistance limits the usefulness of the older class of M2 inhibitors in the setting of circulating influenza.

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This chart shows the approved antiviral drugs for influenza and the influenza types inhibited; routes of administration; the ages for which treatment and prophylaxis are approved; and the original approval dates.

We will be focusing on the neuraminidase inhibitors zanamivir and oseltamivir. Zanamivir is available as a powder for inhalation and oseltamivir is

available as an oral dosage form, as a capsule and a suspension.

The antiviral drugs for influenza were approved for treatment of acute, uncomplicated influenza based on symptom improvement and for prophylaxis based on a reduction in laboratory-confirmed influenza, illness in a community and household exposure setting.

Labeling claims were based on demonstration of safety and efficacy from adequate and well-controlled trials that met established regulatory standards. Information available through literature reports, though not suitable for labeling, could be useful in designing additional studies.

I would like to point out at this time that it is not known what the magnitude of effect will be of these drugs against a novel strain. Some experts suggest that higher doses or longer duration might be needed, but this is beyond the scope of the studies supporting the current approvals.

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What are some of the considerations in MedKit design and study? How much of which products, which

formulations, and which dosage strengths should be included in a MedKit? Should the MedKits be dosing for an individual or household, and what age groups should be included? Should the MedKits be for treatment, post-exposure prophylaxis or outbreak prophylaxis?

What are some of the expected mechanisms for prescribing, dispensing, instructing and tracking usage? What are the provisions for monitoring resistance emergence and adverse events?

It is expected that we will have advisory committee discussions, as we are having today, as part of the development process and the NDA review process once all of the information is available from the studies.

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Let’s talk about the potential study types. Labeling needs to convey accurate understanding of the risk/benefit and usage options. We recommended formal label comprehension studies and actual use studies. In informal label comprehension studies the user needs to decide when and how to use the product.

A clinical algorithm is under development as part of labeling for the MedKit. The clinical algorithm raises

additional questions. Can the algorithm identify the appropriate target population, and can users follow the algorithm as translated into labeling?

With regard to the actual use studies, the user will have to be able to retain the drug through at least one flu season and answer appropriately pandemic scenario questions. These study types will be elaborated upon by CAPT Shay and the sponsors.

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In addition, with regard to the respective antiviral products, that is, the neuraminidase inhibitors, we recommended the following two studies. A home preparation mixing study for Tamiflu, can the user make and dose the liquid preparation from Tamiflu capsules and adjust for changes in a child's size? In addition, we recommended for Relenza, can the user follow the device instructions without a hands-on demonstration?

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What might be learned from the recommended studies? Well, the listed studies may show which parts of the proposed instructions are understood by a range of potential users. They may show what elements of

instructions need to be clarified or retested, and whether study subjects can keep the drug unused at home through a flue season.

[Slide]

What might not be learned from the recommended studies? From a clinical perspective, the listed studies cannot address the accuracy of diagnosis, administration and physician-patient communication in an actual emergency. The studies cannot address the effects on viral resistance emergence, recognition and management of bacterial complications, adverse event occurrence and monitoring. So, additional studies may be needed and we will be seeking your advice on these.

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I just wanted to briefly introduce the topic of resistance, and this will be discussed in much more detail later. Influenza undergoes frequent mutations. The variants are resistant to the older M2 inhibitors and these variants arise rapidly during treatment. They are transmissible and pathogenic. Consequently, the M2 inhibitors are no longer recommended by CDC for circulating influenza.

From the oseltamivir registrational trials, some patients, especially children, shed virus with resistance mutations after treatment initiation. It was not clear if these post-treatment variants could spread to others and cause disease.

What have we learned since then? As you may be aware, there are recent multi-country reports of oseltamivir-resistant H1N1 virus in untreated persons with influenza illness. This report provides new information on the ability of some resistant strains to circulate in association with flu-like illness. Much less is known about resistance related to zanamivir.

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I would like to sum up the differences between the current options and the MedKit before proceeding to the agenda and the questions. With regard to the current options for the marketed neuraminidase inhibitors, both neuraminidase inhibitors are available by prescription. However, the patient generally is evaluated by a prescriber at the time of intended use.

The labeling is for influenza but not specifically for a pandemic situation because it is not possible to

determine what strain of influenza will emerge as the next pandemic strain and there is uncertainty about antiviral effects against novel strains.

With regard to the MedKit, this would be a new use and the instructions have not been previously tested. It would utilize the IND mechanism because new studies and labeling need to be developed to be able to convey the evidence base and the risk/benefit for all the components of the MedKit. Under the IND mechanism, studies will be developed and initiated such as labeling comprehension, etc.

For the MedKit the NDA supplement pathway will be pursued. The current advisory committee is to provide advice regarding the development process and we will be presenting results, once studies are completed, to a future advisory committee.

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With regard to the agenda, following my remarks, we will hear from Dr. Tegeris and BARDA regarding the influenza MedKit initiative. This will be followed by Dr. Tim Uyeki, from the CDC, who will present epidemiology of seasonal and pandemic influenza. Dr. Frank Hayden will present his perspective on treatment and prophylaxis of

influenza. This will be followed by a discussion of influenza resistance by Dr. Klimov, from the CDC. CAPT Shay will present an overview of consumer studies.

We will then take a break, and this will be followed by company presentations from GlaxoSmithKline and Roche. Following that, we will have five-minute presentations from the professional societies before breaking for lunch. There is an open public hearing but if no one has signed up we will proceed right to the advisory committee discussion and questions.

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Here are the questions for the committee: Please comment on the concept of a prescription influenza antiviral MedKit intended for use during a pandemic. We are asking you to specifically address potential risks and benefits for individual consumers and the U.S. population if prescription MedKits were approved with the intention of home stockpiling.

Question number two will be a vote question: Will the phase 3 clinical trials that supported the approvals and favorable results from the proposed consumer use studies allow for safe and effective use of MedKits by individuals

who may not be under direct medical supervision at the time of antiviral drug use? If no, what additional studies are needed?

[Slide]

Question three asks you to comment on the use of a MedKit for treatment versus prophylaxis of influenza during a pandemic, taking into account the characteristics of the drugs included in the proposed MedKits.

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Question four addresses the Tamiflu MedKit proposal with regard to the instructions for dosing children, whether or not the 75 mg adult capsules should be used even though there are other formulations available, including 30 mg and 45 mg capsules as well as an oral suspension. So, we will be asking what is the most appropriate formulation to be used for pediatric dosing.

We will also be asking you in question five to comment on specific elements of labeling, packaging and instructions.

[Slide]

Question six relates to additions or modifications to the proposed label comprehension studies, simulated use

studies and any other additional studies that would help to assess risk/benefit, including what is a reasonable percentage of study subjects who should understand the various components of the labeling.

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The last questionB-hopefully, we will have time for thisB-is, please comment on the type of availability that would be best suited to provide MedKits to the American public and state your reasons. If availability without a prescription is considered, please describe any additional studies that would be needed to support a switch from prescription to nonprescription availability. Thank you very much.

DR. McGOWAN: We will now proceed to the presentations. Before the presentations, I would just like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Our fist speaker in this next section is John Tegeris, from the Department of Health and Human Services, who will talk to us about influenza antiviral drug MedKits:

HHS perspectives.

Influenza Antiviral Drug MedKits: HHS Perspectives

DR. TEGERIS: Good morning. I first want to thank Dr. Cox and Dr. Birnkrant for the opportunity to provide this quick overview and to share with you HHS perspectives.

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Before I start, let me just give a bit of proper framing. I think as we become more knowledgeable in our efforts for pandemic preparedness, we really think that the antiviral MedKit is a strategy that can help us more effectively accomplish our tasks. With the mantel pieces of public health and public safety in mind, we think the MedKits, in the end, properly developed, thoroughly and methodically, can ultimately, if a pandemic occurs and if there is substantial uptake, help to reduce morbidity and mortality and ultimately save lives. So, that is important to keep in mind as we move forward.

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Part of really what guides us as an important theme for the MedKit program is the this mantra of shared responsibility. In the National Strategy for Pandemic Influenza, NRHHS pandemic influenza plan, that was issued in

November of 2005, the story really begins here. In terms of pandemic influenza preparedness, shared responsibility is a key element for successful preparedness and response, and the stakeholders for this shared responsibility really include not only federal and state governments and businesses and communities but individuals, and that is what we are really focusing on here with the antiviral MedKits.

A quote that is taken from HHS Secretary Michael Leavitt during one of his state summits that I really think speaks to this, the efforts we are trying to accomplish is the following: AAny community that fails to prepare with the expectation that the federal or state government will rescue them will be tragically mistaken,@ and this is about personal preparedness and, again, what the MedKits address.

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In the national strategy there are two antiviral goals that are stated. The first is to stockpile 75 million treatment courses for pandemic treatment of 25 percent of the population in the event of a pandemic. The second goal is to stockpile a cache of six million treatment courses for limited containment at the onset of a pandemic.

If you forget about this six million for a moment,

what we have, of the 75 million for the treatment goal, 44 million are coming from the federal stockpile. The other 31 million are coming from state stockpiles that participate in the federal subsidy program. Where we currently stand is that on schedule or ahead of schedule we have stockpiled 15 million treatment courses so the federal stockpile is complete. We have achieved 23 million of the 31 million goal collectively with the state stockpiles having claimed that total portion of their subsidy allotment. So, we have a total of 73 million of the 81 million and that represents achieving 90 percent of our program goal which, considering all the moving parts, is certainly something that we view as an accomplishment but there are gaps.

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As we move forward and we learn more and we become more knowledgeable, obviously we have talked about containment and treatment, we start to focus our attention on prophylaxis of healthcare and emergency service providers and post-exposure prophylaxis to control outbreaks in closed settings. This is really, when we are looking at the MedKits for treatment and prophylaxis, where we can help in this capacity.

We have also taken measures with regard to helping businesses stockpile when you are looking at continuity of operations and how important that is. Both Roche and GSK have unveiled corporate leasing programs to allow business to more easily and more effectively address this issue of stockpiling for their key personnel and, obviously, other personnel. We, at HHS, are very close to issuing to the public guidance on employer stockpiling.

[Slide]

Back to this 25 percent treatment goal, when you break it down per state, this represents a bar graph of all the states. I mentioned that 44 million or 15 percent of the 25 percent goal is accomplished through the federal stockpile and that is complete. But the remaining is dependent on states to make decisions to claim their subsidy allotments.

We see some that have stockpiled more, claimed more, added additional subsidy. We see some that have met the goal and we see a varying amount, from none up to most of the subsidy claim for some states. In the interim, our MedKits can really help to address this gap. In addition--again, this is a treatment goal--some state plans call for

the stockpiles to be used for prophylaxis and that can widen the treatment gap even further.

[Slide]

Concept of personal preparedness, obviously in general we are looking at home stockpiling of medical countermeasures to allow individuals, again, choices for personal preparedness, and not only against pandemic influenza but man-made and natural disasters and other diseases.

Again, what we hope to accomplish is that through the MedKits we really can extend the total amount of antiviral drugs in communities to narrow the gap in terms of total available supply, and really extend the life of the public stockpiles as you move your way through a pandemic.

The other key point is we expect that the MedKits will help to reduce the burden on public health and healthcare systems, knowing that emergency departments, hospitals, healthcare providers are going to be overwhelmed in the event of a pandemic which will slow diagnosis and slow prescribing for treatment to take care of sick people.

Coupled with that, few states really have detailed plans for stockpile distribution and rapid dispensing and

MedKits serve as a very important and vital community mitigation measure. Again, the MedKits really have to have proper messaging in terms of product and usage instructions, and we will talk about that later.

I think another part of this is that home stockpiling of the antiviral drugs not only allows individuals and families to prepare but it increases resiliency and recovery so that the response can not only help people recover faster, it also, in effect, can slow the spread during a pandemic.

[Slide]

We talked about the MedKits in development, obviously, the Roche Tamiflu Medkit and the GSK Relenza Medkit. This is just a snapshot, just to give you all a quick look. We are working together and there have been a lot of effective joint meetings between Roche, GSK and our working groups to work on a MedKit booklet that will accompany in the MedKit the antivirals that will not only talk about a pandemic and talk about product information but working on this algorithm, that I will explain later, that will help people with how to make the right decisions in terms of proper use.

I think the founding father and what planted the seed for the antiviral Medkits is the antibiotic MedKit, the anthrax MedKit which is the generic drug doxycycline. In 2006 CDC conducted a study in St. Louis, a compliance study, to look at home stockpiling of the anthrax MedKit. What that study showed is a 97 percent compliance rate in terms of not using it inappropriately and being able to retain it. There was about an 85 percent response after the study that those people involved would home stockpile and would pay a certain price to do so.

So, it was a successful study and, in the absence of any scientific data to really stop us on this path forward, we think that, you know, this model would work for the antiviral MedKits and that is why we are embarking on this path.

[Slide]

A quick fact sheet in terms of the antiviral MedKit program, obviously licensure is anticipated for use in home settings for adults and children. Adults have to make decisions for children, certainly down to a certain age, and obviously for the elderly in the homes that will need that help.

Again, personal preparedness is key to the program. Not necessarily uptake; it is really about access and availability. The current program will require a prescription to obtain the MedKit. Each MedKit will contain one regimen that can either be used for treatment or prophylaxis.

At the appropriate time HHS will issue a guidance document closer to licensure about home stockpiling for individuals. Currently both antiviral drugs MedKits in development have a five-year or greater expiry which currently applies to the public stockpiles only.

It is important to note that on a small scale we do see kind of home stockpiling with, for example, the Peace Corps where these volunteers who travel abroad do carry a stash of anti-infectives that they have either in their homes or at their site of work. So, this model is in play to some extent.

[Slide]

All right, the challenges. I think we have heard this at FDA and it really is a complex challenge we have with the MedKits and the regulatory path because it really represents a hybrid model of a cross between a prescription

and over-the-counter environment. So, we are working very carefully to develop the best path forward so we can address this.

In June we held an antiviral MedKit workshop and we did a lot of modeling. It was a successful meeting and what we really learned from the modeling in the meeting is that there are concerns that arose from that meeting. One of them is obviously the concern over distribution inequities. I think the business realities we are dealing with is non-generic drugs that obviously are more expensive in that framework. So, that is the concern for distribution inequities. We also have a concern over inappropriate use; obviously, adverse events; and, as Debra mentioned, increased resistance due to antiviral MedKits.

The other thing, and we are not there yet, that we are going to have to deal with is that state pharmacy laws reallyB-you know, you see it on your bottles Adiscard after one year.@ When we are looking at home stockpiling for an extended period of time this is an issue we are going to have to grapple with. Certainly, when you are looking at home stockpiling for extended periods proper storage and retention of the Medkits becomes an important consideration.

[Slide]

In terms of how do we do this and increase safe and effective use? Obviously, a supplemental NDA will have to be submitted with new packaging and new labeling for home stockpiling for pandemic use only.

We talk about, and I will get to it in a subsequent slide, instructions for when to use and not use a MedKit. I think one of the things we are working on is a diagnostic algorithm with an emphasis on patient safety, really to drive people immediately to seek medical care if they need it. So, we will discuss that.

Obviously, the industry studies that Dr. Birnkrant mentioned will be going on, and the label comprehension studies. Recognizing that this is a complex model, you know, we learn as we go and I think it may require a series of pilot studies to really accomplish the label comprehension effectively. That may lead to bringing the experts back in at various times to discuss new topics as new data and new information arises so we may see the need for additional advisory committee meetings over time along this development path.

[Slide]

The algorithm. Dr. Benjamin Schwartz is here. He works with NVPO and is stationed at CDC. He has done a great job leading the charge with his influenza division to develop the algorithm, together with public health partners, medical societies, as well as with our HHS working group. So, it has been a collective collaboration and this algorithm is really designed to mitigate the risk of inappropriate use; allow people in a simple way to effectively use the MedKits when they have to be used.

What it should allow for is diagnosis and either treatment or prophylaxis for oneself or a family member. It affords the individuals the opportunity to determine, again, do I or one of my family members need immediate medical care, do I initiate treatment or prophylaxis, or do I do nothing.

Also, we have worked to make sure the messaging and communication is proper. We have worked with industry partners and contract research organizations that conduct these types of studies to help us best define the algorithm and messaging in the booklets.

[Slide]

This is just giving you a quick outline of the

algorithm, just a quick sense of a visual of what we are talking about. It will be different in the MedKit booklets but basically it drives individuals to certain decisions and helps them in the process. Are there severe signs of illness? Call 911. You work your way down, signs of influenza? Are they present? Yes? Open your MedKit and use your prescription or contact the hotline. This is just a visual of what we are trying to work on.

[Slide]

With respect to the timeline, we started this process back at the beginning of 2008 with the first deputy secretary meeting and invited Roche and GSK to come in to really present on the topic, and to really invite them to take on this challenge for the MedKits. I think both have really embraced it in the interest of public service and public health to embark on this path.

We had the workshop, as I mentioned, in June and we learned a lot. There has been a lot of public outreach going on that Ben has been leading. There has been a lot of interaction between the industry partners and FDA throughout the process.

We hope that with further recommendations of the

advisory committee here we will be in a position that the industry partners can start the first pilot study for label comprehension sometime before the end of this year. And, this open spot is really for what we think will be subsequent studies as we learn more, and potentially subsequent advisory committee meetings to answer important questions so we can continue on this path. Hopefully, a year from now in the northern hemisphere with the next flu season we can start the compliance studies or the non-use studies and the simulation studies or, essentially simulating the use studies.

Along this timeline, we hope that really at the end of a two-year process these MedKits will be far enough along that they can submit their licensure package and, hopefully, have the right data to support approval.

So, that is a quick overview. Thank you.

DR. McGOWAN: I think we will be taking questions this afternoon, and we can obviously invite people to come back and respond. John, thanks very much and now I would like to invite Tim Uyeki, from CDC, to come up and give us an overview of epidemiology of seasonal and pandemic influenza.

Epidemiology of Seasonal and Pandemic Influenza

DR. UYEKI: Good morning. Thanks for the opportunity to speak. This is a gigantic topic.

[Slide]

I was asked to speak about seasonal and pandemic influenza as well as a little bit about H5N1. So, I will try and do that very quickly in 15 minutes.

[Slide]

I think people are pretty familiar with influenza in the U.S. We have annual wintertime epidemics. These are caused by influenza A and B virus infections. Peak activity, although we do surveillance at CDC during October through May we usually see peak activity in the U.S. in November through March.

As you know, the severity of the season varies from year to year. In general, there is estimated 5 percent up to 20 percent of the U.S. population that is ill each season and, in general, studies have suggested that seasons that are predominated by influenza by A H3N2 viruses tend to be more severe than those predominated by H1N1 or B.

The impact in the U.S. is pretty substantial. Clearly, there is a lot of school and work absenteeism.

There are emergency visits. There are outpatient visits for uncomplicated influenza. Certainly, complications of influenza lead to hospitalizations and to mortality and, depending upon the severity of the epidemics, sometimes we can have healthcare systems that are overwhelmed even during seasonal epidemics.

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Now, what is driving seasonal epidemics are really small changes in the viruses. The concept of this we call antigenic drift. Basically, influenza viruses of all kinds are continuously evolving in unpredictable ways and these are really due to point mutations in the gene that codes for the surface protein hemagglutinin. Basically, this results in changes so that our immune system, if we have antibodies from vaccination or from previous infection, may not quite be able to protect against strains that have changed. So, this is what is driving seasonal epidemics worldwide. This is why we need to do surveillance year round throughout the world.

[Slide]

This is just some data from four seasons. This is U.S. data. This is the number of isolates that are positive

for influenza and this is week of the year. This is just to show the variability of when the season peaks. This is this last season, >07->08, which peaked really about late February of this year. In contrast, there are other seasons that peaked more in January. We also had sort of a greater frequency of positive test results.

[Slide]

Clearly, influenza epidemics in the U.S. cause big public health problems and one of the reasons we have antigenic drift that can lead to complications for people who have underlying certain chronic medical conditions, particularly those with cardiac and lung disease. We can have people that have influenza virus infection and then secondary invasive bacterial infection, and there are rare complications associated with influenza. We don't have enough time to go into all of these. Basically, these can result in hospitalizations and death.

[Slide]

So, we don't actually test everyone with influenza in the U.S. Not everyone with uncomplicated influenza presents to medical care. Those that present to care are not always tested, nor are those always who are

hospitalized. So, therefore, we have to deal with epidemiological modeling studies, and these have suggested an annual average of more than 200,000 influenza-related hospitalizations per year. What we see is that the highest hospitalization rates are in those in people 65 years and older, as well as people who have certain chronic underlying illnesses. We also see high rates in young children, particularly less than two years of age.

[Slide]

Now, this is just another way of looking at that data just to show that the hospitalization rates per 100,000 person-years by age group is, you know, visually much higher in people 65 years and older. They are high in children less than five but generally pretty low compared to 65 years and older.

[Slide]

Here are some data from a population-based surveillance system in the U.S., called the New Vaccine Surveillance Network. This is five years of data just to show you that here is one season, here, which was much more severe. These are population-based rates per 100,000 children. This was a much more severe season compared to

these other ones.

[Slide]

When you look at a different population-based surveillance system, this is what we call the Emerging Infections Program, this is looking at young children, less than five, as well as those five to 17. The point of this one is that for children five to 17, which is the dotted line, the hospitalization rates are much lower in general than those in children less than five. Again, here is that severe season which was >03->04.

[Slide]

So, in terms of deaths, and I am not focusing on outpatient visits or ER visits; I am focusing more on hospitalizations and deaths here. So, in terms of influenza-associated mortality in the U.S., again, modeling studies suggest an estimated average of around 36,000 influenza attributable deaths per year.

Similarly to the hospitalization rates, the highest mortality is in people 65 years and older, particularly those people who have certain chronic pulmonary and cardiac disease.

We don’t have great data on mortality for

children. This particular study estimated an average of 92 influenza-related deaths among children less than five years. Since >03->04 we have been collecting pediatric influenza-associated mortality data and we have a range since then of 46-153 children that have died from laboratory-confirmed influenza in the U.S. per season.

[Slide]

This is another way of looking at the data. This, again, is respiratory/circulatory deaths per 100,000 person years by age group. This is deaths. So, again, the vast majority or the highest rates of deaths are really in people 65 years and older, and it is much lower as we go younger in age.

[Slide]

Now, just to summarize those who are what we call at increased risk for hospitalizations and death in the U.S., it is really, again, the elderly, 65 years and older, very young infants, people with certain medical conditions, cardiac-pulmonary disease, metabolic diseases, immunosuppression, immunocompromised people that have certain neurological disorders that impair the handling of respiratory secretions, certainly pregnant women, and we

have many problems with outbreaks in long-term care facilities in the U.S. each season.

[Slide]

Now, just to sort of bridge the gap, there are pandemic influenza concerns. There are human infections with novel influenza A virus subtypes that we call pandemic potential. These include both low pathogenic as well as highly pathogenic avian influenza viruses. Clearly, our biggest concern in terms of the next pandemic as highly pathogenic is H5N1 viruses but, clearly, there are low pathogenic viruses that have infected humans, including H7N2, H7N3. There are low pathogenic H7N7 as well as highly pathogenic H7N7 and H9N2 viruses.

One of the things about H5N1 viruses, like all influenza viruses, they are evolving. They are moving targets evolving in different groups that we call clades. Furthermore, some clades are circulating among birds, and wild birds, generally poultry in many countries, many regions of the world. It is primarily a zoonotic disease in humans but with very high mortality.

[Slide]

So, this is a cumulative map of officially

reported poultry outbreaks since 2003 to the World Animal Health Organization. It is probably an underestimate of the magnitude of the problem in birds since then. This is cumulative. It doesn't represent the current situation, it is cumulative.

But this is just to show you the highly pathogenic H5N1 viruses. It is not just an issue in Southeast Asia or Asia but, in fact, the Middle East, Eastern Europe and West Africa are affected, or have been affected.

[Slide]

So, when we look at the global epidemiology of human H5N1 cases, certainly the outbreak in Hong Kong in 1997, 18 cases, there were two cases noted in Hong Kong residents that traveled to southern China in early 2003. But since November, 2003 to the present there are officially 387 reported H5N1 cases, 245 deaths. That is 63 percent case fatality proportion.

But I would make a point that surveillance for human cases has really focused upon looking for people with severe illness, generally hospitalized pneumonia cases in people that had contact with poultry.

[Slide]

So, this is a depiction of where the human cases have been since November, 2003. It somewhat mirrors where the poultry outbreaks have been so it is Southeast Asia, Asia, but it is Eastern Europe as well, the Middle East and West Africa.

[Slide]

So, the epidemiology of this small number of human casesB-again, this is not really a large number of cases, but they are very infrequent; they are sporadic. Most of the cases have been previously healthy children and young adults. That is in stark contrast to what we see with seasonal epidemics in which generally we see severe disease in elderly, very young infants, people with underlying chronic conditions. These were previously health children and young adults who had contact with sick or dead poultry predominantly.

We have had clusters. Most of these clusters are cases of two to three. They are mostly among blood-related family members. The largest is seven cases. Most of them, again, is poultry exposure that is thought to be the risk factor. But we have had limited non-sustained human-to-human transmission in some clusters and third generation

spread likely in two clusters. But there is no evidence of sustained human-to-human spread. Therefore, we have no H5N1 pandemic and we are in the WHO pandemic alert period phase 3.

[Slide]

Now, why did I present that? Because certainly antigenic shift which is, in fact, the emergence of a new human influenza A virus subtype that has to have a new hemagglutinin so that is H5. It is not a human virus right now.

This can occur through two means, either genetic reassortment between human and animal influenza A viruses. It can occur through direct transmission, in this case with H5N1 virus from poultry to human transmission. That doesn't mean we are going to have a pandemic.

A pandemic can occur if we have efficient, and really it has to be sustained, virus transmission. So, we don't have sustained H5N1 human-to-human spread. So, when we have pandemics theoretically everybody is susceptible. Therefore, we see widespread morbidity and mortality worldwide and a high proportion of deaths. Particularly, it can be among young adults and, again, people who have little

or no immunity.

[Slide]

So, if we look back at the last century and the three pandemics, everyone is familiar with the 1918-1919 emergence of H1N1 estimates. Anywhere from 20-100 million deaths worldwide; in the U.S., probably more than 600,000 deaths. Overall, the case mortality proportion was two percent.

Now, in the H2N2 pandemic of >57->58 there are estimated 70,000 excess U.S. deaths. Then, the pandemic, with much milder emergence of H3N2 in >68->69, with about 34 excess U.S. deaths. H3N2 viruses continue to circulate through antigenic drift.

[Slide]

Why did I present all that background about H5N1? Because there is evidence that the H1N1 virus that caused the 1918-1919 pandemic was a direct mutation from avian influenza A virus, and subsequently the pandemics in >57->58 were reassortments between human and low pathogenic influenza A viruses.

Some of the key genes, including the hemagglutinin, came from an avian virus. So, historically,

in the last century we have direct mutation from an avian virus or we have reassortment between human and avian influenza A viruses causing a pandemic virus.

[Slide]

So, it is very important to pay attention to the reservoir of all influenza A viruses which are in bird species. We have had these pandemic scares. That is what I would call it, or certainly virus infections of pandemic potential in humans with H5, H7 and H9 viruses really since >96->97.

[Slide]

Here is I think a well-known mortality curve. This is deaths per 100,000 population by age. I particularly call to your attention this green line, here, which is the 1918-1919 pandemic. So, in the U.S., you know, there was an increased death rate in young and elderly but particularly striking was the increased death rate in people really 15-35, which is not something we observe during seasonal epidemics.

[Slide]

Martin Meltzer of CDC has done a projection. He published this in 1999. This is using rather conservative

projections. The impact of the next pandemic on the U.S. with a range of up to 200,000 deaths up to 730,000 hospitalizations, 42 million outpatient visits, and an impact of anywhere from $71 to $166 billion. That was based on a range of attack rate from 15-35 percent.

Now, clearly, during pandemics we see high attack rates in children, but we see high attack rates in all age groups. And, these were very conservative estimates.

[Slide]

Now, if you look at differences in severity of the next pandemic-Bagain, we don't know when that is going to be; we don't know what virus; we don't know how severe it is going to be but some estimates have been done for planning purposes. What about a much more severe pandemic?

So, if you look at estimates of a 1918-like pandemic, very severe or category 5, the projected number of U.S. deaths is much, much higher than, say, a more mild pandemic which some of the early estimates have been based on. This is this pandemic severity increase, and really what it is, is an increase in the number of deaths.

[Slide]

This is another way of looking at it. Again,

different categories. This is the 1918. These are more milder pandemics. So, you can see that case fatality certainly goes up; excess deaths go up; illness goes up.

[Slide]

So, another way to look at this is to compare a moderate pandemic, >57-like to more severe. We see that illness and outpatient visits will be similar but look at the big increase in hospitalizations, 9.9 million for a very severe pandemic; a very high number, almost 1.5 million, requiring ICU care; almost three-quarters of a million requiring mechanical ventilation; then more recent estimates of 1.9 million deaths.

So, again, it depends on the severity of the next pandemic which we cannot predict, but it makes sense for a range of severity estimates in terms of planning purposes.

[Slide]

Just to summarize quickly, it is pretty clear that annual epidemics of influenza in the U.S. are a major public health problem. The severity varies from year to year. We have an average of more than 200,000 hospitalizations and more than 36,000 deaths just from seasonal influenza from complications in the U.S. The groups that are at greatest

risk of complications, hospitalizations and deaths are elderly, people with certain underlying chronic diseases, particularly chronic lung and cardiac disease. Rare influenza pandemics clearly can cause very high morbidity and mortality worldwide and will cause this in the U.S. in the next pandemic. Thank you.

DR. McGOWAN: Thanks very much, Tim, for that rather sobering overview of the epidemiology. Now I would like to invite Dr. Fred Hayden to come up and perhaps cheer us up a little bit with an overview of treatment options in influenza.

A Perspective of Influenza Treatment and Prophylaxis

DR. HAYDEN: Good morning and thanks to the organizers for allowing me to participate in this important meeting.

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My goal is to provide really some personal perspectives on the antivirals that will, hopefully, inform the evidence base that will allow you to make the decisions that you have been asked to take today. I have tried to select specific publications from the literature to illustrate some, I hope, relevant points with regard to your

deliberations.

[Slide]

Dr. Birnkrant has already summarized the available anti-influenza agents. The neuraminidase inhibitors have been available now for nearly a decade for management of influenza A and B virus infections and, as she said, are currently approved for treatment of uncomplicated disease presenting within two days of symptom onset.

You will note here, of course, that there are differences in the approval status with regard to age, particularly with zanamivir being approved in somewhat older age cohorts. This relates largely to the inability of young children to use the Diskhaler device in a reliable fashion. That is something to consider with regard to home MedKit application.

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Now, I need to, of course, remind you about the mechanism of action of these agents. The neuraminidase inhibitors block dysfunction of the viral neuraminidase, which is specifically to cleave the terminal sialic acid residues which form the receptors recognized by the influenza hemagglutinin. By doing so, they then prevent

release of virus from the infected cell and spread within the respiratory tract to initiate subsequent rounds of replication.

This slide was provided courtesy of Dr. Graeme Laver, and I specifically chose it because, as many of you know, Graeme recently passed away, in fact, en route to the European influenza meetings in Portugal. He was instrumental in the study of the crystal structure of neuraminidase and in the development of the drugs that we are talking about today, and I think it is important to honor his important contributions to the field. I also need to honor his legacy in that he was an unabashed proponent of having these drugs on everybody's medicine shelf as well.

[Slide]

With regard to the neuraminidase inhibitors, the fact is, of course, that they have not been studied in a pandemic situation. However, we do have information from past studies in both the Hong Kong pandemic in 1968 and then the pandemic-like event in 1977 through the reappearance of H1N1 viruses to show that in the context of seasonal prophylaxis studies.

The numbers are summarized in this table for you,

in fact, the older drugs, the M2 inhibitors, can provide significant levels of protection against influenza A illness, averaging across various studies about 60-70 percent. A lesser effect is seen on protection against serologically confirmed infection, averaging about 30 percent. This just tell us that the bulk of the effect of these drugs is to reduce the illness attack rate, still allowing some clinical immunizing infections.

These kinds of data then establish the principle that it is possible to use antiviral drugs to protect individuals against a novel influenza strain in an immunologically naive population.

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In studies of seasonal influenza prophylaxis even higher levels of protection have been seen when the circulating viruses are susceptible to the M2 inhibitors and, of course, to zanamivir and oseltamivir as well.

We also have substantial databases to indicate that this strategy for seasonal prophylaxis in largely immunized at-risk and elderly populations these drugs are quite active in terms of protecting against influenza illness.

I will spend a bit more time talking in detail about the household-based studies of post-contact prophylaxis, but will simply point out two facets here. One is that the range of protection seen with the M2 inhibitors is quite variable, and this relates largely to the problem of emergence of drug-resistant viruses and transmission which Dr. Klimov is going to address in more detail.

And, in nursing home studies where we have observational studies of termination of outbreaks, the only head-to-head study that I am aware of was the comparison between inhaled zanamivir and oral rimantadine given for 14 days. In this particular study zanamivir had 61 percent better efficacy than rimantadine in protecting individuals against illness, largely because of problems with resistance in the rimantadine cohort.

[Slide]

Now, the household-based studies with the neuraminidase inhibitors are summarized here. There have been four, two with oseltamivir, two with zanamivir. In one instance with each drug the index cases were given the same antiviral treatment that was used for prophylaxis of the household contacts.

The duration of dosing for post-exposure prophylaxis ranged from 7-10 days. You will note the number of contacts here is large in these studies, but there is a difference in design in terms of the age groups that have been included. Two zanamivir studies have individuals 5 years and above. One of the oseltamivir studies focused on teens and older adults.

Across all these studies there have been highly significant reductions in secondary influenza and illness, ranging from roughly 70 to as high as 90 percent, and the 95 percent confidence intervals are indicated here. This is specifically in households where the index cases were proven to have influenza infections so that we know that there was an introduction of virus into that particular household.

As seen in the seasonal prophylaxis studies, the reduction in influenza infection is lower, and this is based primarily on serologic evidence of infection so that the major effect is to reduce illness in the contacts and not so much impact on subclinical infection.

[Slide]

These studies have also allowed us to determine that the drugs are not only highly effective for post-

exposure prophylaxis, and this is a valid way to protect individuals, but also that there has been good tolerance and compliance. Overall, the compliance rates with drug administration have been in excess of 95 percent.

In these studies the withdrawal rates across the board, again, are low, at about the one percent level, with both oseltamivir and zanamivir. With oseltamivir, when used for prophylaxis, there has been an excess of gastrointestinal side effects, nausea, and in this study where children were included, emesis overall occurred in about a five percent frequency, although it was higher, about ten percent, in the young children who received oseltamivir prophylaxisB-again, a consideration with regard to tolerability in these populations.

In the zanamivir studies there really have not been problems with regard to bronchospasm that I am aware of. There was one pneumonia event in an index case, beginning on day four of treatment.

[Slide]

It is worth noting that recruitment strategies were used in these trials because this impacts on this issue of self-diagnosis to some extent. In none of these trials

was self-diagnosis actually done. The individuals were recruited through either clinic-based strategies or with prospective monitoring of households, beginning before the influenza season.

But with those kinds of strategies where there are health professionals involved at one level or another, the proportion of index cases documenting the influenza positive was reasonably good, ranging from 43 percent to as high as 62 percent in these trials. So, in conjunction with some professionals there have been reasonably reliable rates of empiric diagnosis, subsequently proven by laboratory techniques to be influenza positive.

Also, in two of these studies the contacts were cultured before initiation of post-exposure prophylaxis and low frequencies of positivity were noted. But, clearly, there were infections, of course, already initiated after introduction of virus into the household setting.

[Slide]

There are a couple of points to keep in mind with regard to post-exposure prophylaxis. First is that a lot of the events occurred quite early. This is the zanamivir data, published by Arnold Monto, in which over half of the

secondary cases in the zanamivir recipients occurred within two days and 36 percent in the placebo recipients occurred within that two-day time frame. So, again, early initiation of prophylaxis is going to be key in terms of providing optimal protection in an epidemic or certainly a pandemic setting.

[Slide]

Another point to consider is the efficacy of post-exposure prophylaxis in the pediatric population. I have broken out the data in our study of oseltamivir by age. This is the teen and adult population where efficacy was quite good.

But you will note that with decreasing age, particularly in the youngest age cohort here, there was a suggestion, although you will note that the confidence intervals here are extremely wide, that there might be diminished prophylactic efficacy. This is something that may need to be visited in future studies. Another issue here, in this particular study, is that all of the index cases received antiviral treatment with oseltamivir.

I want to show that in the families where the contacts were put on observation to look at subsequent

events there were still very substantial rates of influenza-proven illness, eight percent in the teens and adults and up to 36 percent in the very young cohort.

So I think this tells us that treatment of the index cases, although it may have some effect in transmission of virus, still does not prevent dissemination within the household setting. It is an important issue with regard to some of the modeling studies regarding treatment effects.

[Slide]

Let me turn to treatment then just for a few moments. I think that all of these drugs have been shown to have benefits with regard to symptom relief. I think there are other data though that deal with the more important endpoints with regard to function recovery and prevention of complications. With both of the neuraminidase inhibitors there are I think good data to support the conclusion that they can reduce antibiotic use, particularly for lower respiratory tract events.

The ranges here reflect differences in the ages of the populations under study. For oseltamivir there is evidence for associated reductions in the hospitalizations,

whereas we don't have sufficient numbers for zanamivir. And, I will try to show you some data that support the conclusion that treatment of viral complications is possible.

With regard to this issue of reduction in transmission, an older study did show about a 30 percent reduction in influenza infection in the household contacts of index cases treated with amantadine or rimantadine. We are still uncertain about this effect with the neuraminidase inhibitors because there hasn't been a formal prospective study of this particular question although some derivative analyses suggest an effect with oseltamivir.

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One of the consistent findings across the studies has been the important effect of time to treatment with regard to symptom benefit. In these studies the primary outcome has been time to alleviation of illness as defined by resolution of fever and other symptoms coming down to either mild in severity or absent on a sustained basis.

In our initial studies of inhaled zanamivir we found that the target initiation of treatment had a big effect with regard to the duration of illness after

initiation of therapy. So, those that were treated within three hours after symptom onset had a three-day benefit with regard to resolution of illness, whereas, those treated later had only a one-day reduction of illness severity. In larger studies with oseltamivir, also confirmed, there was also an important effect of time to treatment.

[Slide]

This slide summarizes an analysis of a number of clinical trials examining inhaled zanamivir effects on complications and antibiotic use. Antibiotics reduction was noted for any event to be 28 percent overall with a non-significant effect on upper respiratory tract events, but a clinically important effect, 40 percent, on lower respiratory tract events, primarily with reductions in acute bronchitis. Again, such reductions I think would be important in terms of benefits to not only the patients but also to the healthcare system in general.

[Slide]

One of the issues with zanamivir, of course, is the concern about bronchospasm. This is the current wording in the labeling where it states zanamivir is not recommended for treatment or prophylaxis of influenza in individuals

with underlying airways disease such as asthma or chronic obstructive pulmonary disease. Of course, these are highly prevalent in the population. Certainly, reactive airways disease will be present in many individuals who might be potential candidates for drug use in a household setting.

[Slide]

I just wanted to share the results of one particular study done in a randomized, controlled fashion, involving a very large cohort of ambulatory patients, most of whom had asthma and were treated with zanamivir or placebo. Sixty percent of these were retrospectively then shown to be influenza-infected. And, the time to alleviation of illness with no release medication use showed a significant benefit of two and a half day reduction.

More importantly, the reason I wanted to show you these data is that there was overall tolerance so that there were lower respiratory tract adverse events in the zanamivir recipients compared to placebo; low discontinuation rates in both groups. Hospitalizations were low in both groups.

Importantly, in terms of objective measures, no differences in spirometry on days 6 or 28 after enrollment into the study. About ten percent of both groups had 20

percent or greater falls in FEV1 on day six when they were seen. In fact, when peak expiratory flow rates were tested by the subjects themselves they tended to improve more rapidly in the zanamivir recipients compared to placebo. So, these kind of data are important I think in terms of considering potential outpatient use.

[Slide]

Turning to oseltamivir then, here again there are good data with regard to aggregate analysis involving several thousand individuals with laboratory-proven influenza showing reductions in use of antibiotics for lower respiratory tract complications, with roughly a halving of such events.

In addition, and not surprisingly, there is a reduction in the hospitalizations for any reason. Although the numbers here for analysis are quite small, but they suggest that either in healthy or at-risk individuals there is roughly a halving of such events when there is early treatment in an outpatient setting.

[Slide]

One of the important target groups, again, in consideration for household-based treatment would be young

children. The one study that I am aware of that has really looked at this with oseltamivir is summarized here for you where we enrolled nearly 700 children between the ages of 1-12 years presenting with influenza-like illness with that two-day window. As it turned out, nearly two-thirds were influenza positive, and the benefit here, again, in terms of alleviation of illness was about a day and a half reduction in duration of illness, which represented a 26 percent effect size.

Fewer complications were seen, with reduction of antibiotics overall of 24 percent and fewer new acute otitis media diagnoses, which were reduced by 44 percent with oseltamivir use. Treatment was associated with gastrointestinal side effects, as might be expected, and excess emesis with oseltamivir occurred with about six percent greater frequency. But overall there were few withdrawals due to adverse events in this particular study, although slightly higher with oseltamivir.

[Slide]

An important issue with regard to, again, the transmission question is how rapidly viral loads can be reduced. In this particular study, looking at levels of

infectious virus in nose and throat swabs we found that there was reduction in both placebo and oseltamivir recipients during the first two days of drug therapy, although there were no important differences in a subset analysis involving roughly 80-90 subjects in each group.

It really took several more days before there was a substantial antiviral effect that was obvious with regard to oseltamivir. You will note that by day six virus levels had come down to basically below the levels of detection by this assay.

There are other studies that have looked at this, and it does vary from season to season and virus type and subtype. But in general, these young children, who I think serve as a useful surrogate for what one might see in infections by a novel strain, again, in a naive population suggest that the initial antiviral effects will not be rapid with therapy with single agents.

[Slide]

There have been a number of observational studies with oseltamivir to look at other important outcomes in a nursing home population. There is one retrospective study found reductions in complications, hospitalizations and

mortality with early treatment. There have been studies in high risk leukemia and stem cell transplant patients to suggest lower mortality with oseltamivir treatment compared to no treatment.

In a large insurance database study that included outpatients with influenza-like illness, aged one year and older, treatment with oseltamivir overall had a point estimate of 26 percent reduction in hospitalization for any cause in the month after an influenza diagnosis compared to an untreated group.

Your handout summarizes a number of other observational studies from these large insurance databases to suggest reductions in hospitalizations or sometimes pneumonia events, depending on a particular population examined.

[Slide]

An important consideration, of course, is whether treatment makes a difference later, after that early window. There have been two published studies that I am aware of to try to address this in the hospitalized adults. The Toronto Invasive Bacterial Diseases Network, headed by Allison McGeer, did a prospective study of over 300 adults

hospitalized with community-acquired influenza in a two-season study in Ontario. They used laboratory-based surveillance to identify patients and then went to the bedside to prospectively collect subsequent clinical events data.

So, this was a non-randomized trial. But, as it turned out, about a third were treated with oseltamivir. The vast majority of these were rapid antigen test positive and, of course, this can be a surrogate to indicate relatively high levels of viral replication, and it probably was one of the factors that led to the decision to treat by the physicians who were caring for them. But you note here that the time to treatment was greater than 48 hours in 71 percent and over three days in nearly half of these individuals.

[Slide]

In her multivariate analysis oseltamivir therapy was associated with very significant reductions in those going on to have a fatal outcome. The absolute 15-day mortality was just under four percent with oseltamivir compared to 10 percent without treatment. These kinds of data suggest that even delaying antiviral therapy in

hospitalized patients appears to be beneficial but, clearly, we don't have a prospective, randomized trial yet to definitively answer this particular question.

[Slide]

Another retrospective analysis comes from the Chinese University in Hong Kong where Nelson Lee was able to look at outcomes in over 350 patients, most of whom had confirmed influenza A infection. Those who received early treatment with oseltamivir, shown in the green here, had a two-day reduction in their mean length of hospital stay compared to either no treatment or later therapy.

So, there are these kinds of data coming out and there were some additional presentations at the recent ACAC DSI meeting to suggest benefit in hospitalized patients as well.

[Slide]

Perhaps the strongest test of an agent like oseltamivir or zanamivir would be use in the H5N1 infected patients. This is an infection associated with very sustained, high level replication. Aggregated retrospective analyses now suggest that we are seeing mortality reductions in this cohort.

So, without antiviral therapy, survival in presumed clade 1 or clade 2 infections is quite low, averaging about ten percent overall. With oseltamivir therapy this improves to about 50 percent with clade 1 infections, a little bit lower with clade 2. So, there are these kinds of data then to suggest that treatment in such populations can make a real difference in terms of improving outcome, although still, despite therapy, only about half of these patients will recover.

There are a lot of reasons for this, but the most important appears to be delayed time of administration, or most of the benefit in terms of survival is occurring in those who can get treated within a four- to five-day window.

[Slide]

Just to summarize some of these comments then, early neuraminidase inhibitor treatment reduces illness duration and lower respiratory tract complications in seasonal influenza. Oseltamivir treatment appears to reduce all-cause hospitalizations and perhaps severity and sequelae in those who are hospitalized.

It also shows some benefit in H5N1 patients but time to treatment and resistance emergence are important

variables. I know that Dr. Klimov is going to discuss this in more detail. With H5N1 as really the paradigm of a novel infection then, unfortunately, we don't have data with inhaled zanamivir.

I haven't gone into this but modeling studies predict that substantial reductions in pandemic influenza impact, in terms of the frequency of illness, could be achieved at high levels of household-based treatment and prophylaxis could be initiated in a timely fashion. Dr. Lipsitch has been involved in many of these modeling studies and I am sure he can comment in more detail for you.

[Slide]

I was also asked by Dr. Murray just to comment briefly on what is coming down the pipeline. There are a number of potential targets of interventions with regard to candidate antiviral drugs. Of course, the ones that I have mentioned have focused either on these early ones or the neuraminidase inhibitors. You will note that even in this simple scheme there are multiple other potential points for intervention.

[Slide]

There are, to my knowledge, a series of agents,

which I tried to capture on this table for you, that are currently in clinical development. Older studies with zanamivir given by an intravenous route show that it was highly protective in experimentally-induced influenza. Zanamivir has the advantage of being active against the most common oseltamivir-resistant mutations seen in N1- and also N2-containing viruses. So, it is one that we are hoping to take forward in terms of clinical trials within the Southeast Asia Influenza Clinical Research Network in H5 patients with severe human influenza.

Peramivir, another Neuraminidase inhibitor, given by both intramuscular and intravenous routes of administration has in initial phase 2 studies. There was a trial of the intramuscular form given on a once daily basis that suggested that when there was adequate delivery of the drug by the intramuscular sites a significant benefit, although this needs to be confirmed again because the overall population did not have a significant reduction at the time because of problems with drug delivery.

At the recent ACAC meeting we learned that with intravenous administration in outpatients there were significant effects both on clinical recovery and antiviral

effects. There has been the recent completion of enrollment of a study of intravenous peramivir in a hospitalized population. So, those data are of interest.

A long-acting neuraminidase inhibitor which has this designation, given topically at the respiratory tract, has recently completed phase 2 testing where a single dose given to influenza outpatients was compared to oral oseltamivir. The press release that came out this summer said that the results were rather comparable and this agent is said to be moving forward into phase 3 trial currently.

Another neuraminidase inhibitor, known as T-705, is in the midst of its phase 1 studies in the United States. It has completed those in Japan and phase 2 studies looking at its efficacy in outpatients with influenza are currently in process.

There are a couple of other interesting targets, including an agent that blocks re-attachment of influenza viruses and one that is largely an immunomodulator. The agents are currently in phase 1.

So, there are some things that may make a difference in the next three to five years, particularly looking at neuraminidase targets so that gives us some hope

that our armamentarium will improve as we go forward. Thank you very much for your attention.

DR. McGOWAN: Thanks very much, Dr. Hayden. Our next speaker is Alexander Klimov, from the CDC, who will be talking about influenza resistance.

Influenza Resistance

DR. KLIMOV: Good morning. Thank you very much for inviting me to participate in this very important meeting. Probably we need to move rather fast now. Two classes of drugs, you know, are licensed for control or prophylaxis of influenza.

[Slide]

There was quite a lot of information about one of them, which is adamantanes, or M2 blockers.

[Slide]

The essential points I would like to mention are that those drugs are not active against influenza. Resistance develops rapidly after treatment. And, we do have, and I will show this, quite a high prevalence of resistance among circulating human influenza H1 and H3 viruses. There are some adverse effects and now these drugs are not recommended for treatment of influenza A.

[Slide]

What happened actually? This is for seasonal influenza H3N2 viruses. Approximately before the year 2000 the level of resistance among shield influenza H3N2 viruses was reasonably long, but after 2000 we started to observe an incredible increase in the proportion of resistance, first of all, in China and later on in many other countries, including the United States and Europe. So, since 2005 CDC advises not to use the drug.

But what I would like to point to, to bring to your attention is that, not this season, 2007-2008 but the previous season, >06->07, we had sort of a temporary decrease in resistance for amantadine, rimantadine.

[Slide]

What was the reason? The reason was that among H3 viruses in that season we had several genetic groups co-circulating, essentially four major genetic groups. Only two of them, which we conditionally called Nepal/921-like and Brisbane/10/07-like groups were resistant. The other genetic groups were sensitive to amantadine, rimantadine. During this season A/Brisbane/10/07-like viruses won. They became predominant. That is why we have again an increased

proportion of H3 viruses resistant to amantadine, rimantadine. Brisbane/10 is the current vaccine strain, by the way.

[Slide]

So, what is happening with influenza A H1N1? Again, in China the percentage of resistance among H1N1 viruses is essentially 100 percent. So, it is variable in different countries. In the United States among H1N1 viruses we have approximately 10 percent of drug resistance.

[Slide]

Again, resistance among H1N1 viruses depends on the genetic grouping of the viruses. In this case, again, this is a phylogenetic tree for the hemagglutinin and you can see that only so-called sub-clade 2C, this genetic group of H1N1 viruses, contains an amantadine M2 blocker resistant isolate. The most predominant group, which is 2B, does not have virus resistant to amantadine, rimantadine. But this group, and we will talk about this, contains viruses resistant to oseltamivir.

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Also, the use of adamantanes likely contributed to the initial emergence of resistant variants. Other factors,

like antigenic drift and gene reassortment, appear to contribute to the global spread of adamantane resistant H3 and H1 seasonal viruses.

[Slide]

What do we see among H5 influenza viruses? Again, resistance among influenza H5 viruses depends on the genetic group or clade. So, here you can see only clades for which there are human cases documented and clade 1 to viruses which were in circulation mostly in Vietnam, Thailand and Cambodia. This clade seems to be declining in recent years. All human viruses are resistant to M2 blockers. Approximately 93 percent of avian viruses from this clade are resistant to M2 blockers.

Clade 2 can be divided into major three sub-clades. Actually, there is a more complicated classification of clades now. Sub-clade 2.1 includes all viruses from Indonesia. On average, this sub-clade has 83 percent resistance. But if you take viruses of recent two or three years, they all are resistant to M2 blockers.

Moving to sub-clade 2.2 and sub-clade 2.3, sub-clade 2.3 are viruses which are circulating prevalently in China, some of them in Vietnam and that region now. Sub-

clade 2.2 are viruses which are geographically more spread. They came to Europe, Africa, some other Asian countries.

Generally speaking, at most those sub-clades are sensitive to M2 blockers. Sub-clade 2.2 has approximately one percent resistant viruses; sub-clade 2.3 has approximately five percent of resistant viruses. Other clades on average have a percentage around 17 percent of resistance.

[Slide]

So the mutations, there is one specific mutation within the M2 protein which is a target for action of adamantanes, which is responsible for resistance in most cases.

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Resistance to neuraminidase inhibitors.

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What I would like to mention here, in addition to what was said about neuraminidase inhibitors, is that structurally neuraminidase inhibitors mimic the natural enzyme substrate of neuraminic acid. Zanamivir, which was designed a little bit before oseltamivir, was designed according to the so-called minimalist approach. Zanamivir

mimics neuraminic acid pretty tightly. Oseltamivir, due to this lipophilic group, has more differences from the original substrate.

Also essential is that both the zanamivir and oseltamivir drug design was based on the structure of two subtypes of the neuraminidase, N2 and N9. During the development of both of those drugs only those two sub-type crystal structures were available.

[Slide]

And, the nature of resistance to neuraminidase inhibitors is drug dependent. Essentially, it is drug dependent and, as we will see a little bit later, sub-type dependent.

Essentially, there are two groups of mutations which can lead to resistance to neuraminidase, mutations in the frame work within the active site of the neuraminidase and mutations around the catalytic sites within the framework. So, catalytic site and the framework. Mutations at the catalytic site, one of them was typical for H3N2 viruses, they confer resistance to both oseltamivir and zanamivir because they are within the region of the active site. But mutations in the framework usually cause

resistance in oseltamivir but not always in zanamivir.

[Slide]

This is piece of crystal structure for neuraminidase of N1 subtype and of N9 subtype. As I mentioned, the drug design was based in 1999, actually before 1999, on the crystal structures of N2 and N9 neuraminidase. Here you can see that the neuraminidase of the N1 subtype has a wider hole which should adapt the neuraminidase inhibitor, or which includes the analog of the sialic acid.

[Slide]

There is little or no resistance emergence to zanamivir in treated patients but, you know, zanamivir is used much less than oseltamivir right now. Emergence of oseltamivir resistance in treated patients was shown to be quite low in adults, and later on it was shown that in children it could be up to 18 percent. That was a study in Japan. About 9 or 50 kids who were treated with oseltamivir and shed resistant viruses. Reduced transmissibility and infectivity of neuraminidase inhibitor resistant viruses was observed, but the degree of reduced transmissibility is mutation specific.

[Slide]

So, CDC monitors influenza A and B virus susceptibility to zanamivir and to oseltamivir, and right now over 100 viruses are tested. Before 2007-2008, there were was less than one percent of resistant viruses, viruses resistant to neuraminidase inhibitors within the United States. In Japan, during this four-year period, it was approximately one percent. But you know that Japan is using quite a lot of oseltamivir right now.

Beginning with the 2007-2008 influenza season, a marked rise in oseltamivir resistance was observed in the United States and in other countries.

[Slide]

This is a map which is as of July 1, at the end of the winter season, northern hemisphere season. You can see that the geographic distribution of H1N1 resistant viruses was quite broad.

[Slide]

Interestingly, the level of resistance was different, for example, in Europe for different European countries, from essentially zero through about 70 percent, 68 percent in Norway. I have to emphasize that Norway is

one of the European countries which is almost not using neuraminidase inhibitors.

So, this data and other data show that oseltamivir-resistant mutants appeared not because of the level of use of this drug. So, in the United States at the end of the season we had approximately 11 percent of resistance. In Canada, Canada had approximately twice as high a level of resistance to oseltamivir.

To compare to China, it was about 11 percent; Australia 4 percent; 2 percent in Japan percent as of May of 2008. This is what I mentioned before, Japan is using quite a lot of oseltamivir in recent years but, as I said, the level of resistance in Japan is quite low, around two percent.

So, we can conclude that the frequency of resistance was not related to country use of oseltamivir. As I mentioned, in Europe, for example, 68 percent and 67 percent in Norway with no use of oseltamivir, and in Japan about two percent.

[Slide]

Again, genetically the resistance to oseltamivir depends on the genetic group to which H1N1 viruses belongs

to. As I mentioned the 2C subgroup, which is M2 blocker resistant, and the 2B subgroup, which is predominant now, this subgroup has some proportion of oseltamivir-resistant viruses. All those viruses have the same mutation, histamine to terazine at position 274 if we are using N2 neuraminidase number and N1 neuraminidase number, and this is to the 275 position.

[Slide]

Resistance in the U.S. and in Europe in 2007-2008, we tried to follow-up the cases for which isolation of resistant viruses were documented. You know, at this stage of the study approximately 100 patients, 99 patients with documented oseltamivir resistant H1N1, none of them took oseltamivir prior to testing. None of the household contacts were taking oseltamivir prior to their onset of illness.

When compared to illness cause by oseltamivir-sensitive influenza H1N1 viruses, essentially there was no difference in clinical illness and severity of illness, and approximately the same risk groups were affected.

Similar results are available from Europe. It doesn’t look like there is a difference in the clinical

manifestation between sensitive and resistant H1N1 viruses.

[Slide]

The geographic distribution within the U.S. was also not even. So, you can see that the majority of states did not have resistant viruses but some of them did have resistant viruses. But you should also take into account, please, that the 2007-2008 season in the United States was predominantly an H3N2 season, in contrast to Europe where H1N1 virus was predominating.

[Slide]

Here I would like to compare the situation for the influenza season in the northern hemisphere and the influenza season in the southern hemisphere. This data from WHO is as of October 13th. Let me not go through all the details, but for Europe in total we can see that during the winter season we had approximately 25 percent of resistance in influenza H1N1 viruses. And, I would like to repeat once again that resistance among H1N1 viruses was observed to oseltamivir only. All oseltamivir-resistant H1N1 viruses are sensitive to amantadine or rimantadine. All the viruses tested so far are sensitive to zanamivir.

The number of samples tested in Europe is small

but the proportion seems to be increasing. In Asia during the winter season we had approximately five percent of resistance to oseltamivir and now, again a much less number of samples, but the level is about 16 percent.

[Slide]

In Oceania has essentially the influenza season right now. During our winter season they had approximately 1.5 percent of resistance. Now they have about 82 percent. And, some countries like New Zealand, New Caledonia, reported 100 percent of resistance to oseltamivir; Australia, 80 percent of resistance. Of course, New Caledonia and New Zealand has a very low number of viruses tested.

Please pay attention to the Republic of South Africa, 225 samples were tested. All of them are resistant; Senegal, only 10, 100 percent of viruses resistant. So, the total in Africa is about 88 percent versus 3 percent during our winter season. But the number of cases was very low.

Americas: We definitely see a tendency to increase in the proportion of resistance within the South and North American countries. In the U.S. our most updated results are about 12 percent of resistance. Among 7 viruses tested

between the end of the North American season and now we had 3 resistant of them. So, the global level of resistance to H1N1 viruses is about 16 percent now.

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What do we have among H5N1 group of viruses?

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First of all, I would like to bring your attention to the fact that the so-called IC50, the concentration which causes 50 percent reduction of the neuraminidase activity, which is the measure of influence of the drug on the neuraminidase, this figure depends on the clade or sub-clade.

I will give you just one example. If you compare clade 1, which has an IC50 within this range from 0.02 to 0.8, which is about 40-fold difference between the lowest and the highest one within this group of viruses, you can see that the sub-clade 2.1, which is Indonesian viruses, has on average approximately a 10-fold reduced sensitivity to neuraminidase inhibitors. So, as I mentioned, the resistance to neuraminidase inhibitors is not only drug dependent; it is also subtype dependent and, even worse, sub-clade dependent within the clades.

[Slide]

This is particular mutations which are known for converting viruses to resistance to oseltamivir in this particular case. I will draw your attention to a recent case we found, one mutation in position 117, and we have pretty solid evidence now that this resistance existed in poultry samples and later on most likely was transmitted into humans.

[Slide]

So, fitness of oseltamivir-resistant H5N1 viruses also depends on the drugs and depends on the particular mutations. In the ferret model in one of the studies clade 1 oseltamivir-resistant mutant 274 was viable, but it had 10-fold lower titers in lungs.

In a murine model, in a mouse model, in a paper published recently, clade 1 resistant viruses were generated using genetics and both caused a lot of infectivity and infectivity was actually unaltered and those mutants were as virulent as non-mutant viruses.

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So, the current status: We cannot exclude that H1N1 may come to the United States and to other countries

during this season. All oseltamivir-resistant viruses have the same mutation in the neuraminidase gene. They are sensitive to amantadine and rimantadine. As I mentioned, approximately 10 percent of H1N1 viruses are resistant to M2 blockers but they are from different subgroups. All are sensitive to Relenza.

In the United States, if you take all viruses influenza A H1N1, influenza A H3 and influenza B, you will find that approximately only two percent of the total influenza viruses circulating this season were resistant to oseltamivir. Obviously, they have been sensitive to zanamivir.

Adamantane resistance among other influenza viruses is very high, as I have said, about 100 percent among H3. Influenza B viruses are majorly resistant also to oseltamivir.

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Consideration for this coming season: Overall prevalence of oseltamivir resistance in the U.S. during 2008-2009 is difficult to predict but it will depend on prevalence of resistance among H1 viruses and prevalence of H1 viruses among total circulating viruses. Virulence of

oseltamivir-resistant viruses does not seem to be different from oseltamivir-sensitive viruses.

There are few options for changing antiviral recommendations if it becomes necessary. We have a limited number of alternative antivirals as of now, and zanamivir, for example and adamantanes, are of limited use due to different reasons right now.

I should also conclude that so far there were not any tendencies to change recommendations, not by the European CDC, not by WHO and not by other professional groups. Thank you.

DR. McGOWAN: Thanks very much. As we are running a little behind schedule we are proposing to actually take a break now and delay our next speaker, CAPT Shay, until after the break. I think we should also maybe reduce the break to about ten minutes.

Can I remind panel members, please, that there shouldn't be any discussion of the issues at hand during the break amongst yourselves or any member of the audience. So, we are going to be starting again at 10:10.

I would also just like to welcome the members of the European Medicines Agency who have joined us by

telephone. We will take a break now.

[Brief recess]

DR. McGOWAN: I would like to introduce CAPT Laura Shay, from the Division of nonprescription Clinical Evaluation, who will be giving us an overview of consumer study design.

Overview of Consumer Studies

CAPT SHAY: Good morning, everybody. I have to say I am glad that the break was given because I think people needed a little bit of a pause before going to consumer studies, which is really switching gears quite dramatically.

[Slide]

As you know, I am the social science analyst for the Division of Nonprescription Clinical Evaluation.

[Slide]

The focus of my presentation is to provide you an overview on consumer study designs, and also to provide an overview of proposed study designs for pandemic influenza MedKits.

Now, for half the room the overview of consumer study designs will probably be just a brief review and for others this will be a real new concept for you as far as

study designs are concerned.

[Slide]

Essentially, there are three types of consumer studies, label comprehension, self-selection and actual use.

[Slide]

The following table provides a listing of the proposed consumer studies for the MedKits. This listing is based on information that we received as of October 6th. The companies have since this time communicated with us but they have made some changes to their development plan which they will present.

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The purpose of a label comprehension study is to determine if written materials communicate the important information about a drug without aid from a healthcare professional. The objectives are to test key communication elements on the label. These are not considered clinical trials. No drug is given.

Ideally, they should be the first phase of a development program. The label may require multiple revisions and re-testing, and it is important to note that the purpose of a comprehension study is to test

comprehension and not behavior.

[Slide]

The target population should be a representative sample of the U.S. population of potential product users and nonusers. Therefore, it should include a low literacy cohort. This cohort should be assessed using a validated literacy testing instrument such as the Rapid Estimate of Adult Literacy in Medicine, which is known as the REALM, and an adolescent version which is known as the Teen-REALM. There should be minimal exclusion criteria, and the study may be enriched with subgroups of interest.

[Slide]

The questionnaire is the primary data collection tool. It is administered through scripted interviews using these types of questions, open-ended, closed-ended and scenario questions.

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An open-ended question will ask for the answer to be unrestricted and all of the data and responses are recorded and coded.

With a close-ended question the participants choose an answer from a restricted answer set such as

multiple choice or a yes/no. The close-ended questions are generally followed by an open-ended probing question in order to evaluate the correct response and to obtain information on incorrect responses.

The scenario is a hypothetical medical situation to test the ability of the respondent to apply information on the label. These include both closed- and open-ended questions.

An example of a scenario question is this one: Janet is a 38-year-old with diabetes who has a headache. This would be the scenario. Is it okay or not okay for her to take medication X? A close-ended question. Followed by the open-ended probing question, why do you say that?

[Slide]

So, in summary, label comprehension studies determine if consumers can understand key elements in the written material. However, they may or may not predict behavior in an actual use study or in the real-world conditions.

[Slide]

Both MedKit proposal plans include label comprehension studies which are testing the following key

communication elements: When to use the MedKit; when not to use the MedKit; who should not take the drug; prevention versus treatment; dosing for prevention versus treatment; and when to seek medical attention.

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Now we move on to self-selection studies.

[Slide]

The purpose of a self-selection study is to assess a consumer's ability to correctly choose a product based on the information on the label. Again, these are not considered clinical trials because no drug is administered. They can be separate studies or combined with label comprehension studies or actual use studies.

[Slide]

The target population is similar to a label comprehension study, a representative sample of the U.S. population including a low literacy cohort. There should be minimal exclusion criteria and, again, the study may be enriched with subgroups of interest.

[Slide]

Here is an example of a testing procedure that is commonly done in a self-selection study. The participant

reads the label and then a self-selection question is asked. For example, is this product appropriate or right for you to use? Followed by the probing question, why do you say that? Demographic information and medical history are collected, and the correct self-selection is based then largely on the self-reported information.

[Slide]

The MedKits are currently being proposed as a prescription product. Therefore, contraindicated us is not initially determined by the individual. However, once in the home, self-selection decisions will need to be made without the assistance from a healthcare professional.

[Slide]

These self-selection decisions are the following: when to take the product for pandemic versus seasonal flu; prevention versus treatment; and if new medical contraindications should arise; and what dose to take for prevention versus treatment, and based on age and weight of child.

[Slide]

The proposed development plans for the MedKits are testing these self-selection decisions. They are not being

tested as separate self-selection studies, however, they are being incorporated into the label comprehension studies.

[Slide]

Now, with actual use studies the purpose is to simulate use of a product in a real-world setting without input from a healthcare professional. The primary objective is to assess adherence to labeled directions and warnings. The secondary is to provide data on safe use of the product in an unsupervised setting. These studies can generally be considered clinical studies because drug is given.

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Depending on the behavior of interest, there may be a variety of different endpoints, for example, failure to follow dosing instructions and failure to seek medical attention when appropriate based on the label.

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The target population should ideally be all individuals who may have an interest in the product, and there should be limited exclusion criteria.

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We recognize that it is difficult to achieve a real-world setting. However, minimal healthcare provider

and/or study personnel involvement should be factored in. We also recognize that there is a very fine line between collecting enough data for a meaningful assessment and collecting too much data and influencing behavior. Data collection methods include diaries, phone interviews and follow-up visits.

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The duration of the study varies depending on the labeled duration of use. It is important to note that an actual use study cannot always predict correct behavior when the product is marketed.

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The proposed actual use studies for both MedKits are the compliance studies in which participants are prescribed a MedKit to take home, and the primary objectives are appropriate non-use of the drug for seasonal flu and the ability to retain and locate the MedKits in their homes.

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Additional actual use studies being proposed are the following: For the Relenza MedKit the study is a human factor study. In a study using only the written instructions participants must demonstrate the ability to

correctly perform all the steps required for safe and effective us of the Diskhaler device.

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For the Tamiflu MedKit, this study is a mixing study. Again, using only the written instructions the participant must demonstrate the ability to prepare the correct dose of Tamiflu for children less than ten years of age using the contents of a 75 mg capsule.

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So, in summary, creating a well understood label and written materials may require multiple revisions and re-testing.

Successful label comprehension studies may not predict correct behavior in an actual use study, just as an actual use study cannot always predict correct behavior when the product is marketed.

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The proposed consumer studies will test comprehension of specific communication elements in the written materials; ability to mix a proper dose of Tamiflu for child less than ten years of age; the ability to properly use the Relenza Diskhaler device; the ability to

locate the MedKit in the home; and not to use the MedKit in the absence of a pandemic flu.

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The proposed consumer studies do not test more complex decision-making that requires the ability to understand multiple label elements at one time: whether the written materials and instructions accurately select the intended population for use during a flu pandemic; the actual use of the MedKits; and behavior during a scenario of a flu pandemic.

[Slide]

So, what we need from the advisory committee members is to help us determine if the proposed consumer testing is adequate and if additional consumer testing is needed. Thank you.

DR McGOWAN: Thanks very much. We are now going to move to the sponsors' presentations. There will be a brief opportunity at the end of both presentations for the committee members to ask clarifying questions. I would like to invite first of all Judith Ng-Cashin, from GlaxoSmithKline, to come up and tell us about the Relenza MedKit program.

Relenza MedKit: Potential Use for Pandemic Influenza and Proposed Development Plan

DR. NG-CASHIN: Thank you.

[Slide]

On behalf of GlaxoSmithKline, we thank the advisory committee and the Divisions of Antiviral Drugs and Nonprescription Drugs for the opportunity to discuss issues around providing the Relenza MedKit for pandemic preparedness and our proposed development plan.

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GSK is responding to a request from the Biomedical Advanced Research and Development Authority of the U.S. Department of Health and Human Services to develop a Relenza home stockpiling product.

Our objective is to respond to BARDA's request by providing an anti-influenza therapy to be kept in the home for use during a pandemic situation in a presentation that maximizes patient safety and antiviral efficacy while minimizing the potential for the generation of antiviral resistance. This objective will depend on the appropriate prescription by the consumer's healthcare provider and the appropriate use by the consumer according to clear guidance

and instructions.

In order to ensure that the Relenza MedKit is a successful pandemic preparedness product critical public health authorities must be highly engaged and involved throughout the process. Specifically, the local departments of health must provide clear instructions for the correct timing of use based on the local pandemic alert phase.

In addition, national public health authorities must provide endorsement of antiviral home stockpiling, as well as guidance and instruction for the local public health authorities so that they may formulate public communication plans that are consistent with an overall national strategy.

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While GSK fully supports all efforts to promote pandemic preparedness, as evidenced by our activities with both Relenza and our pandemic vaccines, we do acknowledge the potential risk of providing Relenza in a home stockpiling product.

Of obvious concern is safety. Relenza has known associated adverse events, including bronchospasm, which in part defined its appropriate patient population. The product might be used by patients for whom Relenza is not

recommended, such as those with underlying pulmonary disease.

Also, an individual's medical status could change between the time the MedKit is dispensed and the time it is used, altering the risk/benefit ratio Relenza provides for that individual. Unsafe storage of the MedKit might result in use by unintended individuals such as children. Of course, there is the potential for inappropriate use of the MedKit during a non-pandemic situation.

While the medical benefit of Relenza has been proven in acute, uncomplicated seasonal influenza through well-controlled clinical trials, the use of Relenza has unknown medical benefit against pandemic influenza, highlighting an efficacy risk.

Consumers could retain or use the MedKit after the product's expiration date, adversely affecting potency. Also, inappropriate storage of the MedKit under extreme conditions theoretically could attenuate the potency of the drug.

Finally, a major concern around home stockpiling of any antiviral for pandemic influenza is that suboptimal use will result in the unintended generation of viral

resistance, further complicating an already dire situation.

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Despite these legitimate concerns, there are many potential benefits to providing a Relenza MedKit for home stockpiling, many of which were highlighted by Dr. Tegeris. Allowing consumers to keep Relenza in their home will provide access to Relenza during a pandemic influenza, providing greater and more immediate access to antiviral medications for a larger proportion of our population. During a pandemic access to healthcare may be severely limited. Drug availability may be quite constrained due to manufacturing capacity being limited. And, distribution plans may be compromised. Home stockpiling of a MedKit would ensure access to Relenza despite these challenges.

Having Relenza ready for use in the home might positively contribute to pandemic containment by maintaining social distancing while preventing the ability of antiviral use to inhibit person-to-person transmission.

Finally, increasing the numbers of patients treated or prophylaxed may improve survival and decrease morbidity, as well as provide a bridge of antiviral coverage while patients await vaccination availability or efficacy.

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Keeping these potential risks and benefits in mind, our objectives in developing the Relenza MedKit are several fold: First, we aim to respond adequately and in a timely fashion to BARDA's request for the provision of antivirals to appropriate lay individuals in advance of an actual influenza pandemic in order to enhance the public's overall pandemic preparedness consistent with the national pandemic strategy.

Within this plan, we seek to protect patient safety through specific use instructions written to define the appropriate patient population, the correct use of the inhaler device in the pandemic influenza situations during which the MedKit should be used.

In addition, we hope that through clear warnings about suboptimal use and instructions guiding appropriate use we will minimize the risk of promoting antiviral resistance.

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Let's take a moment now to review the approved indications for Relenza inhalation powder. Relenza is a potent and highly selective inhibitor of the viral

neuraminidase. Relenza has been shown in well-controlled clinical trials to be safe and efficacious as a treatment and prophylaxis of influenza A and B, and its approved indications reflect these data.

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Several factors contribute to the potential for Relenza to be useful during an influenza pandemic. While there are no direct data addressing the efficacy of Relenza in pandemic influenza, the amino acid sequence that targets within the neuraminidase is highly conserved across influenza A strains, suggesting that the antiviral activity should also be conserved.

In addition, the in vitro activity against potential pandemic strains and the animal model efficacy data against avian influenza A H5N1 support the notion that Relenza should be efficacious against pandemic influenza.

These data have provided enough confidence for the U.S. government to stockpile antivirals to cover 25 percent of our population, as Dr. Tegeris has reviewed. Other governments and private corporations have adopted stockpiling programs as well.

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Because the concept of stockpiling antivirals for pandemic preparedness has been accepted as sound by many governments and large corporations, the potential utility of home stockpiling to widen the protected population is gaining favor. However, concerns remain that the current data do not support a risk/benefit profile justifying home stockpiling of antivirals. Several medical societies and professional organizations have expressed these concerns and we will hear from some of them later on today.

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In order to best discuss the safety risks, we thought it would be useful to review the safety profile of Relenza. During the clinical development program the phase 2 and 3 clinical trials enrolled over 14,000 subjects, over 7,000 of whom received inhaled zanamivir.

The incidence of adverse events within the six phase 3 treatment trials was similar between subjects receiving zanamivir and those receiving placebo. The adverse event frequency within the six phase 2 and 3 prophylaxis studies was similar across all arms.

The most commonly reported adverse events within the development program were consistent with the signs and

symptoms of influenza infection. For special populations including children, the elderly and those with underlying high risk conditions, no differences in safety were observed. There were no differences in the incidence of respiratory or neuropsychiatric events comparing zanamivir to placebo within this development program.

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Since the launch of Relenza in March of 1999 1,408 spontaneous adverse event reports have been received by GSK. The estimated postmarketing exposure worldwide is 7.6 million treatment courses. The majority of the adverse event reports originated from Japan, the U.S., Canada and Germany, and 21 percent of these reports were psychiatric disorders. However, 67 percent of these were reported from Japan in 2007 and 16.8 percent of the total cases fell within the respiratory, thoracic and mediastinal disorders category.

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There was a spike in reports of spontaneous neuropsychiatric adverse events in children and adolescents in Japan during the spring of 2007. This prompted a close review of our own safety data.

During the 2006-2007 influenza season 145 neuropsychiatric cases were reported to GSK. Careful analysis of these data did not reveal convincing evidence of a causal association for accidents, neurological or psychiatric events, including convulsions, loss of consciousness, suicidal ideation, depression or self-harm behavior. These data were reviewed with the Pediatric Advisory Committee in November of 2007 and we have updated the U.S. prescribing information to include information regarding neuropsychiatric events.

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Respiratory adverse events have also been associated with Relenza use. In 2000 spontaneous reporting of respiratory adverse events, especially bronchospasm, prompted a change to the U.S. prescribing information, stating that Relenza is not recommended for individuals with underlying airways disease. This issue and additional clinical data were reviewed earlier by Dr. Hayden.

Since 2001 GSK has undertaken periodic analyses of the spontaneous respiratory adverse event reports. Few cases have been identified, and based on the review of these cases no additional changes to the label are warranted.

[Slide]

Providing Relenza in this home stockpiling presentation raises concerns that suboptimal use within the community could promote antiviral resistance. Let's review the data we do have on zanamivir resistance to further assess this risk.

Zanamivir resistance is difficult to generate in vitro, requiring several passages under high zanamivir concentrations compared to the one or two passes required to generate amantadine resistance.

While difficult in vitro zanamivir resistance has been generated in influenza A, both in human and avian strains, this resistance is conveyed through mutations at positions 119 and 292, as well as through double mutations. However, to date one zanamivir resistant clinical isolate has been recovered. This isolate was influenza B with an R152K mutation, and was isolated from an immunocompromised child who had been treated for 15 days with nebulized zanamivir.

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Oseltamivir resistance has also been observed. Clinical isolates containing the resistance mutations listed

here have been reported. These strains retain sensitivity to zanamivir. Of particular interest is the H274Y mutation in influenza A H1N1.

This oseltamivir resistant strain has been observed worldwide since 2007 and is increasing in prevalence within surveillance samples, as Dr. Klimov has pointed out. The reported prevalence of this strain in the northern hemisphere during the 2007-2008 influenza season was 16 percent and more recently, during the southern hemisphere 2008 winter, was 39 percent, suggesting that this strain is spreading.

The H274Y mutation confers a 800-fold decrease in sensitivity to oseltamivir while remaining fully sensitive to zanamivir. Also, the H274Y mutation has been observed in H5N1 isolates. These data support the HHS recommendations to include both oseltamivir and zanamivir within stockpiling programs.

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Certain compound characteristics affect the resistance potential of zanamivir. Its target is highly conserved and resides in an essential region of the neuraminidase. Also, as Dr. Klimov discussed, zanamivir is

a close mimic of the receptor's natural substrate, making it theoretically less likely to be the subject of a resistance mutation.

The topical delivery of the drug allows for high local drug concentrations at the site of viral replication. Finally, treatment with Relenza has been shown to result in rapid reductions of respiratory viral load, reflecting a rapid decrease in viral replication. All of these attributes impact negatively on known mechanisms of antiviral resistance generation.

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Within the Relenza MedKit development program we seek to address the risks we have highlighted here, stressing the appropriate use of the product in order to ensure to safety while minimizing the risk of antiviral resistance.

The proposed development program is composed of four studies designed around the critical questions that address these risks, and designed to incorporate best practices for studies supporting the home use of this product, as reviewed by CAPT Shay.

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In our development program we will test a preliminary MedKit configuration with the following key components: The Quick Guide that will provide instructions for use of the MedKit as a whole. This will include the self-diagnosis algorithm that is currently under development by the CDC.

The practice Diskhaler, which is the same Diskhaler delivery device used for Relenza, that requires proper assembly but does not contain active drug.

The instructions for us that will provide instructions in how to assemble and use the Diskhaler device. The consumer is encouraged to use the practice Diskhaler in conjunction with the instructions for use.

Finally, Relenza inhalational powder in its commercial packaging will also be contained within the MedKit.

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The four studies in which we will study the preliminary MedKit are the label comprehension study that will answer the question can consumers understand the product's use, directions and warnings in the Quick Guide consumer brochure; a human factor study that will address

the question can consumers assemble and use the device correctly; the compliance study over one influenza season that will investigate if consumers can retain the product and not use it during an active influenza season, and understand its use in a simulated pandemic scenario; and, lastly, the extended compliance study that is needed above the one season compliance study will similarly investigate if consumers can retain the product properly over two influenza seasons.

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So, let's go over these studies individually. The label comprehension study will test the effectiveness of the Quick Guide brochure around key communication objectives, including the MedKit's intended use, its directions for use and its warnings. There will be two study populations, one at normal health literary and one at low health literacy, with each cohort having 175 subjects.

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The label comprehension study is a multi-site, single visit study conducted at market research sites. Consumers will be recruited from the general population through sites within the U.S. Evaluation will occur through

interviews, and no active drug will be dispensed.

The labeling stimuli will include the outer Relenza MedKit carton and the Relenza Quick Guide consumer brochure. Third party scenarios will be used to test comprehension and the rationale for the subjects' responses will be evaluated. These data will be used to further refine the labeling.

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Next, the human factors study will test the consumer's comprehension of the device instructions and the ability to manipulate and use the Diskhaler device correctly. This consists of assembling and using the device according to the Diskhaler instructions for use. That includes nine specific directions that will be evaluated individually.

The study populations will include three cohorts, normal health literacy, low health literacy and parents of children 5-15 years old with evaluation of the child's ability to inhale with the device. Each cohort will have 175 subjects.

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The human factors study is a multi-site, single

visit study. Study subjects will be recruited from the general population and evaluation will occur by observation. No drug will be dispensed. The activities and actions within the study will include assessing health literacy, reading the Diskhaler instructions for use, practicing with the Diskhaler prior to actually using the device, demonstrating the use of the device as they are preparing to use it, observing and reporting behavior, and reviewing the rationale for the behavior and any incorrect actions with the consumer. These data will also be used to improve the label further.

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Next we have the compliance study. This study will be conducted in two parts. First, a three-month retention portion to evaluate the consumer's ability to retain the MedKit and avoid use during an active influenza season. Then, second, a pandemic scenario portion to evaluate a subject's ability to make appropriate use decisions within a verbal pandemic scenario through verbalization of actions that would be taken based on the subject's own judgment and the labeling presented.

This portion of the study incorporates aspects of

the pandemic influenza stockpiling plan being created by HHS, CDC and the FDA. The study population will include a cohort of adults and a cohort of parents of children aged 5-15, each having 150 subjects.

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The compliance study is a multicenter, open-label study that will be conducted in approximately 10-20 clinical research sites across the U.S. over one influenza season. The study MedKit will contain active Relenza.

The labeling stimuli will consist of the exterior package and labeling, the Quick Guide consumer brochure and the Diskhaler instructions for use.

Subjects will be in a state of readiness for an influenza pandemic by storing the MedKit at home with all enclosed instructions, practice materials and brochures. Subjects will be evaluated on their ability to retain and locate the MedKit, and their reasons for use or non-use.

In addition, the subjects will be randomized to one of two verbalized pandemic scenarios and then asked to decide if or when the Relenza MedKit should be used in that scenario, and then asked about the reasons for their decisions based on their own judgment and the labeling

presented.

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If the three-month compliance study is deemed adequate this extended compliance study will not be pursued. If these data are needed, this extended study will run in parallel with the three-month study. The extended study will have the same design as the compliance study that we have just presented, with the following modifications: The in-home retention period will be 15 months instead of three months which will allow for the evaluation of behavior over at least two influenza seasons instead of only one. Also, the pandemic scenarios will not be tested during this extended study.

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To summarize our proposed development plan, we have designed this program to address the identified safety and resistance risks by testing specific instructions defining the correct use of the device and the correct pandemic scenarios for appropriate use. In addition, this program was designed to generate the necessary data required to support the Relenza MedKit being used at home by a consumer without recent input or assessment by the

prescriber.

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In conclusion, GSK is committed to working with the critical public health authorities and the FDA to ensure that the optimal Relenza MedKit containing the necessary labeling and instructions is progressed in order to maximize its potential benefit in pandemic influenza, while mitigating the identified risks around home stockpiling of antivirals.

We feel that the development plan we have proposed here addresses the identified risks and is consistent with the national pandemic preparedness plans of BARDA and HHS. The success of the Relenza MedKit for home stockpiling as a safe and effective option during an influenza pandemic is dependent on the provision of clear guidance around appropriate prescription for healthcare providers and clear instructions defining how and when the product should be used for patients and consumers.

This, in turn, requires both local and national public health authorities to be fully engaged in the development and support of the Relenza MedKit. This will ensure a coordinated and consistent communication and

deployment plan across the country in line with the overall national pandemic preparedness strategy. Thank you.

DR. McGOWAN: Thanks very much, Judith. Can I now ask Michael McGuire, from Roche, to come up and give their presentation on the Tamiflu MedKit?

Tamiflu MedKit for Pandemic Influenza

DR. McGUIRE: Good morning.

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I would like to thank the Division of the Antivirals and the Division of Nonprescription Clinical Evaluation and the members of the advisory committee for the opportunity to discuss with you today the Tamiflu MedKit for pandemic influenza. Dr. McGowan, if you don't mind, there will be some slides I will kind of go through quickly because they have already been covered by other speakers. I just didn't want you to think I was skipping them.

[Slide]

What I would like to do is take you through a brief outline of what we will be covering here: an introduction and overview for Tamiflu; talk very specifically about the MedKits stakeholder feedback we have received. I will talk about pandemic planning, some ongoing

pandemic planning that Roche has been conducting to cover resistance, safety information, and a communication plan. I will spend some time on our proposed studies and our conclusions.

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With regard to introduction, I have a number of my esteemed colleagues here from Roche on the right side of the room. They will be here to answer questions during the Q&A. These members have been very much involved in the development of the MedKit program.

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We also have two external experts, Dr. Dave Bradford from PEGUS Research, the CRO firm that has been working with us, and Dr. Donald Low, Chief of Microbiology at Mt. Sinai Hospital in Toronto.

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Tamiflu is indicated for the treatment and prophylaxis of patients one year and older. As you can see, here is the dosing for Tamiflu. For adults for treatment it is 75 mg BID for five days, and for prophylaxis it is 75 mg once a day for ten days. For children, obviously, it is being dosed by weight. A child 33 lbs and under receives a

30 mg dose; 34-51 is a 45 mg dose; 52-88 is a 60 mg dose; and a child over 88 lbs would require a 75 mg dose. I will come back to this as we talk about the construction of the MedKit with the 75 mg dose that we chose.

[Slide]

In terms of adverse events, you can see the most frequent adverse events, as compared to placebo, in our treatment and prophylaxis studies. Also, we do have since launch some postmarketing serious adverse events. We have had rare reports of skin and hypersensitivity reactions, and we have had the neuropsychiatric adverse events that sometimes have led to injury, which is stated in our package insert. We also note, which is stated in our package insert and has been covered at previous advisory boards, that this is reported in influenza patients with and without Tamiflu use at the current time, and the contribution of Tamiflu to these events has not been established.

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If we take a look at the clinical trials here, first, if we start with the adults, we had a clinical trial for treatment which consisted of approximately 850 influenza-infected adults and 450 influenza-infected

pediatric patients.

The primary endpoint for adults was the time to improvement for all the associated symptoms. There was a score card with seven symptoms that the adults filled out, and we looked at the time to resolution on that. What we did see is a 1.3 day reduction. For pediatrics we looked at time to freedom of illness and we saw 1.5 day reduction in that time period.

I think as you have seen before, some additional data has come out. Dr. Hayden presented that, and some of the additional benefits that are currently seen with Tamiflu.

With regards to prophylaxis, we had approximately 2,000 adults in our study and 200 pediatric patients, and they were enrolled in both seasonal or post-exposure prophylaxis studies. The primary endpoint here is the incidence of laboratory-confirmed influenza in these individuals. What we did see in the seasonal component for adults is an efficacy rate between 76-92 percent, and with regards to post-exposure prophylaxis in adults 68-89 percent efficacy, and in the pediatrics 80 percent efficacy.

That is something for us to keep in mind as we are

thinking about MedKits for use in the event of a pandemic, not only for treatment but also to protect those who are around folks who are infected.

[Slide]

So, the rationale for the MedKit-BI think Dr. Tegeris has done a great job with explaining that earlier, but the key here is it is really going to require individual action and responsibility. What we have seen, and which was identified before, is that federal and state governments have a stockpile of 81 million treatments. At the current time, those treatments are indicated for treatment of influenza.

Recently what we did see, in 2007, was guidelines that were issued by HHS and CDC on corporate stockpiling. It would be very important for us to maintain employee health and to maintain business continuity in the event of a pandemic. We are going to need to make sure we have the food system up and running and the energy system up and running during this time period. So, it would be important for us to protect the employees during this time period.

So, what you can see here is a leveling, if you will, on a national scale with what the government trying to

do. Now we are going to go more local with corporations, and the pandemic MedKit really drives it down to that local level which is where the responses are going to be needed.

The program has really been designed to provide immediate access to antivirals when symptoms first appear in individuals, and reduce the barriers to obtaining these antivirals and utilize them as quickly as possible. During a pandemic it would be difficult for individuals-and I will go into this a little bit later-to probably get antivirals, and it would be difficult for them to actually see healthcare providers during that time period.

[Slide]

WHO has issued some guidance with regards to the role of antivirals in avian and pandemic influenza. What you can see here is very specifically H5N1. WHO states that as the primary antiviral agent or choice, and we have limited observational evidence with this strain, H5N1, that early administration, which is going to be key regardless whether it is H5N1 or any type of strain of influenza-early intervention is going to be very important. It could be associated with reduced mortality in patients.

With regards to overall pandemic influenza, I

think the key here and the question we should be asking ourselves is why stockpile. We want to stockpile because pending the availability of vaccines what we first have to have is a strain of the vaccine that will be circulating so vaccine manufacturers can develop a vaccine. And, that may take a few months for that to occur and the manufacturing process to be wrapped up, and the volume of vaccine that would be needed to treat the millions of Americans.

So, what we will have here is antiviral drugs that will be the principal intervention at that point in time since there won't be another intervention, other than potentially social distancing, masks, and other types of hygiene.

So, stockpiling ensures that you have sufficient supplies because when this happens, and if this happens, what we will see is that neither manufacturers will be able to meet the surge of capacity or the demand that will occur. At the current time we have the ability to produce 400 million treatments of Tamiflu but, as you can see, if a pandemic were to occur that certainly would not be enough to treat everyone or prophylax everyone that we could. So, stockpiling, and that is what you see the governments around

the world doing and the opportunities for corporations to do, is the best way for us to be prepared in the event of a pandemic.

[Slide]

What we see here is some case series from Egypt and Indonesia with the H5N1 virus. I bring this to your attention because it talks to the early intervention in both cases. The sooner we are able to get drug on board, the better the survival. On this axis you see the percent of patients surviving versus the day of onset from treatment or remission. So, in both cases we see that early intervention leads to a better chance or survival in these patients.

[Slide]

Now, there are really two pathways currently available for drug approval. As you know, there is the prescription pathway and there is the over-the-counter pathway. To take a look at a drug that is prescription to move into an over-the-counter pathway, it has to be different in various ways, either by indication, by dose or by patient population.

So, what you see here with regards to the MedKit is, since we are using it for seasonal influenza treatment

and prophylaxis, our indications would be the same, if you will, for a pandemic. You also would have the same indications so far for dose for the patient populations which it would be used in.

So, we don't see a real differentiation with regards to that, and that would lead us to taking a look at some nonprescription OTC-like mechanism that would maximize the access of a MedKit. This would be extremely important for individuals who could not and would not be able to seek a healthcare professional. I think what was mentioned earlier, it could be a hybrid of what we are seeing here today or creation of an alternative regulatory approval mechanism that may be needed for a new kit. This is a new path I think we are all going down at this point in time.

[Slide]

Let me talk to you very specifically about the MedKit. The MedKit consists of the 75 mg capsules. It will be packaged in a carton which looks different than the seasonal packaging that we currently have on the marketplace. Within the packaging is what we call the MedKit booklet. Each package will contain ten capsules, and that will be either for treatment or for prophylaxis. So,

one of these could be used for either treatment or prophylaxis.

[Slide]

I know it is difficult to see this, and you may have it in your handouts, but on the very top what we tried to do is instruct folks not to utilize the Tamiflu unless directed by local public health authority. That would be the first step in the appropriate usage.

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I just want to spend a moment on this because this is I think question four that you will be asked to discuss later on today. We have made the MedKit with one dose of 75 mg. I think as you saw early in the presentation, the dosage that happens for children increases as they get older. The concern we had when we developed this that you would buy the 30 mg capsule of Tamiflu at that child's weight. As the child gets older it is no longer the right dosage for that child. Now what happens is we are potentially under-dosing.

So, by the fact that we took the one dose of 75 mg you are able to adjust that dose by the weight of the child growing older. There will be less confusion with having one

dosage strength there versus three dosage strengths.

Certainly, the other question you may have is what about suspension? Well, suspension has a shelf-life of two years. So, we would have people constantly buying the suspension, versus a shelf-life of the capsules which, at the current time, is five years.

We do have mixing studies, and we have done these studies and have the information on opening the capsules and providing it in different foods, some of them being chocolate syrup, and so forth. We have stability data; palatability data; and we have preservative efficacy as well.

[Slide]

I mentioned to you that there is the MedKit booklet. Now, within that MedKit booklet is what was referred to earlier today as the CDC algorithm for diagnostic reasons. It is developed by CDC in conjunction with some of the same medical societies that will be speaking later today.

Really, what it does is help people walk down the pathway of the signs and symptoms that they may have that would signal to them whether they have flu or don’t have

flu. What it also tells people is that through this process they need to take a look at their underlying medical conditions. If they have seen a physician within the past six months and they have been diagnosed or are on treatment for diabetes or respiratory or cardiovascular type diseases they are instructed to call their physician before starting therapy with regards to either one, Relenza or Tamiflu.

This kit is only to be used and only to be applied once the local health department declares an emergency, and for those family members who have an onset of symptoms that is being diagnosed as an infection they would start it for treatment and the members of the household could take it for prophylaxis. Hence, you would start to implement community mitigation strategies of treating everyone within that area within that household.

[Slide]

There was a meeting, as was mentioned earlier, with regard to HHS and there were some challenges that came up with regards to the idea of a MedKit. We needed to address the burden of the healthcare professional. We needed to address inappropriate use and the timing of the product as well. There were concerns about resistance and

adverse events.

What you see here in the top three is really the objective of the algorithm, really to help us work through that process and take that burden off the healthcare professional by having folks work through and identify whether they have infection or they don't have infection.

It certainly talks about when they should not take it. In other words, they shouldn't take unless the local health department has declared an emergency, and they shouldn't take it if they have underlying diseases. And, the timing of use as well.

Let me talk to you a little bit about resistance. But if what we see as these steps are followed is that the potential for resistance is probably low because the appropriate dose will be used at the appropriate time with the appropriate individuals. I will talk to you a little bit more about what we are doing with regards to adverse event reporting in the event of a pandemic.

At Roche we are going to convene our own scientific advisory board with various members from these associations, starting in January, to continue to develop feedback, information and their suggestions on how we are

moving forward with regards to the development of the MedKit materials, the information and the messages.

[Slide]

Let me switch gears just a little bit for you and go to pandemic planning. These activities are ongoing. We have already started these activities.

The first is an avian flu registry. This is an observational registry of patients with H5N1 infection. It is global, multi-center, and the objective here is to collect information on the clinical course and outcome of H5N1 infections, and also to understand what treatments and dosing regimes are being used in these patients.

The dose prediction model is really a model that combines nonclinical information, seasonal clinical information, as well as H5N1 data. The objective of this is to have the model help us predict what Tamiflu dosage would be important or would be required to suppress viral replication. These are two ongoing activities. We recognize they are important to do to be prepared for a pandemic.

[Slide]

So, resistance: I think you have seen in the

earlier presentation two types of resistance. There is the drug-induced resistance and there is the naturally occurring resistance.

What I would like to talk to you about here is drug-induced resistance. This information comes from our clinical trials that I spoke to earlier today in the presentation. What we did see in the clinical trials--and remember now, clinical trials very well controlled so we were able to follow these patients; we were able to culture these patients-Bwhat we saw was a very, very low level of resistance within these studies.

We have not seen any resistance in our prophylaxis studies which, once again, would be an important intervention in the event of a pandemic. What we have seen with these strains that worries us is the very low fitness and transmissibility to other folks so we have a high barrier of resistance.

[Slide]

This slide that you see here nowB-that was clinical trials, this is actually community surveillance information. What you see from the U.S. here, this was captured by the CDC and Japan information was captured from

the Neuraminidase Inhibitor Susceptibility Network. What we see is a low incidence of resistance across the board here. During this time period there were eight million prescriptions written in the U.S. for Tamiflu, and during this time period there were 29 million prescriptions written in Japan. So, as you can see, a low level of resistance with high prescribing.

[Slide]

The next one is naturally occurring. Naturally occurring resistance may occur with any drug and disappear spontaneously as well. It appears to be driven not so much by drug-induced by antigenic drift.

What we did see in this past season, the 2007-2008 season, and continue to see is an H1N1 strain that is resistant to Tamiflu. Now, this is associated with mutation 274Y as well as additional mutations. If we had the one mutation, the 274Y, it probably would not cause this virus to be transmitted to other people so what we have to have other mutations, and we continue to look at this.

As was presented earlier, there is no apparent relationship to Tamiflu use or exposure in these individuals, and what we have here is the overall prevalence

of resistance of the H1N1 virus. But surveillance is going to be critical for us, continuing surveillance.

[Slide]

So, what we have done is that for seasonal influenza we convened an expert panel to help us with this. To guide us on the resistance data, the generation of the analysis, and communication on what we need to do with this information. We are going to be implementing what we call the IRIS study, the Influenza Resistant Information Study. It will consist of 1,200 patients starting this season, the 2008 season, and will continue to 2011. We are going to evaluate the clinical course in individuals and monitor both naturally occurring and drug-induced resistance to all anti-influenza drugs.

With regards to pandemic monitoring, WHO and CDC currently have a very extensive network for surveillance. We would expect that that would continue during a pandemic and what Roche would be more than happy to do is to work with both WHO and CDC to see how we can augment their activities during a pandemic, should one occur.

[Slide]

Collection of safety information will be

important. We certainly can anticipate an increase in adverse events just because there will be more flu around, if you will, and it will be a proportional increase based on what happens during a pandemic.

So, what we need to do is find a way to capture information from folks in local communities. What we are going to be doing is requesting from healthcare professionals and consumers information to be reported to us. We are going to use the MedKit booklet, which has a 1-800 number and our website on it, to ask them to give us information with regards to what is happening. We are going to use our website. We will also take out radio and newspaper and TV ads to encourage people to report adverse events to us during this time of a pandemic.

What we will do is we will use these mechanisms here. We will ask them to use the telephone, web, e-mail, paper or fax. We are going to try every way to capture this information. Because, once we capture that information, it will be important for us then to aggregate that information and provide it to healthcare authorities.

[Slide]

So, we plan on having continual reporting to

healthcare authorities, starting when WHO declares trigger 5 in a pandemic. What we will do is we will analyze and aggregate the data. We will put a special emphasis on populations that may be of special interest and we will be looking for any new safety signals that may be popping up that we need to provide that information to public healthcare officials in treating and prophylaxing individuals.

We also recognize that there might be a need for urgent communications as well as these continual communications. So, we will need to do that with both patients, with healthcare professionals and other stakeholders. We certainly want to do this in collaboration with CDC and WHO and others so that we have the same, consistent message so one group isn't saying something different versus another group and there is confusion for healthcare professionals out there.

[Slide]

With regards to this communication plan, as I mentioned to you, we want to work with all these groups to disseminate this information. The communications may address a number of different topics. It could be

resistance. It could be safety. It could be dosing. We intend to use various channels to provide this information. Just as we try to capture it coming in, we will use TV, web-based and print vehicles. We are also going to try and work through the medical and pharmacy societies with that information so that they can provide that to their constituents as well.

[Slide]

If I could just take a moment to go through the proposed studies for you, here you see the timeline that we have been working under. We have had continual dialogue and meetings with the HHS and the government working group all throughout this process. As you can see, there was some stakeholder feedback that HHS received in June. We also did some market research at this point in time to make sure we were capturing all the concerns and challenges that stakeholders had.

We did a label comprehension pilot testing study during the September time period. From some of that, we have made changes already to some of our packaging and some of the wording that is within the MedKit booklet. What we are planning to do is to do a full label comprehension

study, which I will talk about in a minute, and a simulation and compliance study.

As was outlined earlier today, we will also be doing a mixing study, having consumers come in, providing them Tamiflu and asking them to mix Tamiflu. We are going to put them in a situation where they would actually be, for instance, in their kitchen and there would be a drawer with different utensils there and they would have to take the right utensils, and we would be observing them during this time period to make sure that they are able to follow the directions as stated in the MedKit booklet.

[Slide]

So, the labeling comprehension study: There will be a standard mall-intercept study. There will be 667 respondents in it, 400 of them with 8th grade and above reading level and 267 below 8th grade reading level.

There will be structured and scenario questions and we will be evaluating the drug facts label. Let me back up because there is one point I left out when I showed you the carton. On the carton itself we have put the drug facts information, very similar to what you would see on OTC type products, for folks to have immediate information on some of

the most important things that they need to know. So, we will be testing that during this. We will also be testing the information within the Tamiflu MedKit booklet at this time. We will be conducting screening and demographic questions as well during this study.

[Slide]

In the simulation and compliance study we will be looking at approximately 2,000 households to conduct this in. So, we take first the simulation study. The objectives of the simulation study are to evaluate the subject's intended actions based on responses to scenarios. So, what we would do there, we would say to individuals, okay, you are in Washington, D.C. and a pandemic has been declared in San Francisco. What should you do? We would ask them, when you picked up the MedKit five years ago you were in good health and now you have underlying cardiovascular disease. What should you do?

So, we will evaluate them in terms of those types of scenarios, and that will be done through a questionnaire with the individuals.

The compliance study, what we will do here is we want to assess the number of intact Tamiflu MedKits returned

relative to the total number returned. So, what we are going to be doing here is very similar to what you heard before from our colleagues from GlaxoSmithKline, put a six-month study out there, putting the MedKits out in influenza season and that will be the real test of whether folks can follow the instructions.

We are going to ask for all the MedKits to be returned at the end of the season and we will follow-up with a questionnaire for them on additional information. We are going to define noncompliance as missing capsules at the end of the study. For instance, if any of the capsules within the blister pack package are missing, we will define that as noncompliance.

[Slide]

So, in conclusion, a couple of things if we take a look at the potential risk and mitigation strategies here. We understand these risks and we are trying to do everything we can, in conjunction with our colleagues in the government, to minimize these risks as best as possible.

So, we know there are the adverse events. There have been 55 million prescriptions of the product written worldwide since 1999 and our safety profile has not changed

drastically from what you saw in the slides earlier in the presentation. We do have and we will continue to build a comprehensive strategy for collecting adverse event reports during a pandemic.

Viral resistance will be important. We will need to monitor this as part of worldwide surveillance initiatives.

With regards to dose, the question will be maybe what is the dose. We have the dose prediction model that will include information on emerging strains, and that is an ongoing activity that will continue.

You know, one of the concerns certainly is incorrect diagnosis or if somebody has a concomitant secondary bacterial infections. What we have seen in some of the data presented earlier is that complications of influenza may decrease with early treatment. That is something we should keep in mind. And, certainly, the CDC algorithm identifies patients with underlying diseases who should not take the drug before they call their healthcare professional. It is stated within the algorithm too that if patients do not get better within 48 hours to do a follow-up with their physician as well.

[Slide]

So, if we take a look at the benefits of it, certainly increased availability will be very, very important for us. Once again, stockpiling is the best way to have that availability because when, and if, a pandemic occurs we will not be able to meet that surge capacity. By having the MedKit in the home we can decrease the burden on the healthcare system and we can decrease it on providers, and folks could begin to treat themselves in their homes and not go to the hospitals which could put an extra burden on the system.

It also helps with regards to social distancing. The idea here is to keep people from seeing each other, and what we know is that in a household if somebody has an infection they can treat themselves. They can prophylax the family and it will certainly help with the idea of social distancing and community mitigation. The key here is will be empowering individuals and households to really prepare for a pandemic in terms of protective measures.

As I mentioned to you before, we are also going to have a delay in potential availability of a vaccine. So, the antivirals will serve as a medical intervention that

could be used during that time period.

[Slide]

If you take a look at some of the modeling that has been done for household stockpiling, and you heard earlier that we have 81 million courses of therapy, if we were to increase the number of antiviral regimes we could prevent more deaths and we could prevent more hospitalizations by increasing this and using the antivirals for prophylaxis as well as treatment.

[Slide]

What you see here is information with regards to the H5N1. We do see by using antivirals a better survival rate, 47 percent versus 12 percent of folks that were not treated, once again demonstrating the impact that antivirals make on the influenza infection.

[Slide]

So, finally in conclusion, the Tamiflu MedKit, we believe, addresses very clearly unmet public health needs. We support and want to work with the agency to identify the optimal regulatory mechanism to maximize access to the Tamiflu MedKit. We recognize that it may be a pathway that is not readily available at this point in time.

We want to continue to work with HHS, CDC and FDA to implement the right development program as we are moving forward and, as you can see just in summary, we do have studies already ongoing to help us with pandemic planning, the IRIS study; our enhanced AE collection. We also have the avian registry that we talked about.

Once again, the key will be here with all of this information, AE information as well as other information that comes out of resistance studies, consistent collaboration with CDC, FDA and WHO so that we can make sure we get this information out to healthcare authorities as well as the public. Thank you for your time and attention, and I would be happy to take questions.

DR. McGOWAN: Thank you very much, Michael, for that presentation. We now have the opportunity for clarifying questions for the companies. So, I would turn to my colleagues on the committee and ask if there are any questions. We have our first question on the right.

Clarifying Questions for the Companies

DR. BRASS: I only have seven pages of questions but I think I will save some for later. First of all, I would like to disclose for the record that I am a consultant

to GSK on unrelated projects, just for the record.

I have a couple of clarifying questions that will help me better understand some of the risk to benefit of this proposition. First of all, the prophylaxis strategy is based on a household index case and is designed for ten days of prophylaxis. What is the rationale for that as compared to a community-based, longer duration once the pandemic has been declared in the community rather than waiting for a household member? What was the basis for that decision?

DR. McGOWAN: It would be helpful if you clarify who you want to direct the question to.

DR. BRASS: Anybody who knows the answer.

DR. McGUIRE: We certainly would be more than willing to work with that suggestion.

DR. BRASS: Well, it is not a suggestion because I don’t know the answer. But it seems that you are going to recommend ten days of duration based on an index case that should be based on some assessment that that is an optimal strategy compared to any other strategy. For example, you have data on 40 days of prophylaxis, or one of the two sponsors did, in another setting. So, why the ten-day strategy versus a 40-day community-based strategy? Again,

it should be data driven, not whatever you think.

DR. NG-CASHIN: For Relenza, the data we do have on prophylaxis is within household and contact prophylaxis over a ten-day course. We do have safety data with Relenza prophylaxis over 28 days currently that would support that length of a prophylactic course. We are in the midst of starting a trial to investigate longer-term prophylaxis, over two to four months, anticipating that this is a need that we might have in the case of pandemic influenza.

At this point, you know, we see the interaction being a prescription for a particular individual for either treatment or prophylaxis, and it was hard for us to understand how we could individualize a community-based strategy given the point of contact as the patient-physician or patient-healthcare provider prescription.

DR. BRASS: I have a yes/no question, just yes/no, for each sponsor. In your compliance studies do you require the participants to purchase the kits?

DR. McGUIRE: No.

DR. NG-CASHIN: In our compliance studies, no.

DR. BRASS: There is a bunch of information in the consumer material, patient material, that seemed to have

some relevance in a physician setting but less relevance in the individual patients being prescribed it. For example, why is it important for the patient to identify whether or not they have heart disease and/or diabetes in their decision whether or not to use the product?

So, my point here is this is not a zero sum game. Information you put into the consumer materials is going to diminish the value of other information. So, any information that has to be there really has to be there. And, there was a bunch of information, and I will talk more about this later in the afternoon. But specifically what is the rationale for listing heart disease and diabetes as reasons not to use the product?

DR. NG-CASHIN: My understanding is that that is within the diagnostic algorithm, and that is still under development. There is an overall strategy that we wanted to make sure that the patient reassesses his or her medical condition prior to using the MedKit.

DR. BRASS: But why should a diabetic not use it?

DR. McGUIRE: Part of that information is actually in our label. Just to echo, this is the information that we were provided with regards to the work being done on the

algorithm so we put this into the booklet this way. I don't know, Dr. Schwartz, do you want to comment?

DR. BRADLEY: John Bradley, from Children's, San Diego. There is a recurrent theme here on the duration and the doses for both treatment and prophylaxis, and it is all based on epidemic seasonal influenza. That is all the data that we have. The current package label is a starting point for where we go for pandemic influenza. The dose may be different. The duration may be different. Prophylaxis may be longer.

And, what they are presenting is prophylaxis for family exposure. Is ten days long enough? We don't know. We won't know until a pandemic is here so that information won't get to the families early in the epidemic, certainly. But I am looking at ten days as a place to start. The community prophylaxis issues in a pandemic are completely different issues and I think need to be addressed separately, and it is confusing enough to have one kit for both treatment and family prophylaxis, let alone another kit for community prophylaxis. But your point is well taken.

DR. McGOWAN: We have a question from Dr. Lipsitch now.

DR. LIPSITCH: Yes, two clarifying questions. One is on slide 38 of the Roche presentation. The slide states HHS modeling for government and household stockpiling and reports massive prevention of deaths. It is dated May 28th which, to my knowledge, is prior to the completion of any work on household stockpiling. So, is it possible that that is actually just government stockpiling models?

DR. McGUIRE: I am sorry, your question is, is it possible that that is a misprint? I can't access that website but my guess is that that actually reflects government stockpiling models rather than household stockpiling. I will ask my colleague, Dr. Micky Salgo to help you.

DR. SALGO: Actually, in the modeling data as put forward in that reference, they include government stockpiling and then separately home stockpiling, including treatment and prophylaxis, so that column does include treatment and prophylaxis. Could I have the slide up, please?

[Slide]

Here you can see the three columns as described in the draft HHS guidelines that have gone through the review.

So, the treatment alone is on the left-hand side; post-exposure prophylaxis, as described, is in the middle column; and treatment and post-exposure prophylaxis, the benefit seen, is in the right-hand column.

DR. LIPSITCH: I think those models reflect prophylaxis in the household but from stockpiles that are publicly maintained rather than maintained in the household.

DR. McGOWAN: We actually have representatives here from HHS. I wonder if someone would like to clarify for the committee the model.

DR. SCHWARTZ: Thank you. My name is Ben Schwartz. I am with the National Vaccine Program Office. These estimates are from HHS modeling and they represent the use of antiviral drugs for treatment and prophylaxis, but they do not say where the drugs come from. So, if a public sector stockpile drug is used for treatment or prophylaxis it would have the same impact as if that drug were maintained in the household and used correctly for that same indication.

DR. McGOWAN: I think there is a question from Dr. Murata, on the left, first of all.

DR. MURATA: I have a question for both sponsors

and it is in two parts. First, as proposed for these pandemic kits, besides the wording which essentially, it is my understanding, says do not use unless a pandemic is indicated, are there any other strategies or methods to dissuade the use of these kits for seasonal influenza for household members that may potentially self-diagnose and self-treat for seasonal influenza?

DR. NG-CASHIN: At least in the Relenza MedKit there will be language that is repeated throughout the exterior carton labeling and the Quick Guide brochure for consumers, and we hope that this language is clear. But beyond that within the kit we are not providing any other disincentive, I guess, to not use it during seasonal influenza or a situation that might be a cold for instance.

DR. McGUIRE: With regards to the Tamiflu MedKit, if I could have slide up, please? You have that information on the cover of the booklet itself. You also have the instructions to stop before you take this. Slide up, please.

[Slide]

Here is an enlargement of that stop; wait till the local health department has declared it. It is on the

package on the outside and you see it on this booklet. If I could have the next slide up, please?

[Slide]

On page five of the booklet we clearly indicate not to be used for seasonal influenza, only for pandemic. Much of this wording you will see in bold. One of the things we need to make sure, both sponsors, is that the information is exactly the same, if you will, with regards to algorithm. It will be different, obviously, versus the product. But we are working real hard to make sure that we get the algorithm part of this exactly the same so we don't have confusion at that point in time.

DR. MURATA: Following the converse, the other part of the question that I had was, aside from that last statement as shown on the last slide of the Roche presentation, guidance for seasonal influenza is to potentially see your physician.

DR. McGUIRE: I am sorry, I couldn't hear you.

DR. MURATA: Essentially for seasonal influenza it is not to be used, and then the only guidance that is provided in both kits is essentially to see your healthcare provider.

DR. NG-CASHIN: That is correct. Just to follow-up on the first point, besides coordinating between the two companies around the correct messages about how to appropriately use the MedKit, it will also take a concerted effort within the other governmental agencies involved in this whole pandemic preparedness strategy. We would hope that message will be consistent and strong throughout all the messages that the consumer and patient might receive.

DR. McGUIRE: And we will be testing that, obviously, through the labeling and comprehension and the simulations as well, testing what both companies will be doing. So, we will try and make sure that people don't get the wrong answers, if you will.

DR. McGOWAN: I am feeling slightly like an auctioneer at Sotheby's. I apparently have a list of 12 people waiting to ask questions, or thereabouts. So, I would like the questions to be extremely short and focused and limited to one question, and responders, you please be extremely focused and short so that we can have a balance of questions and answers. The next person on my list is Dr. Benowitz who had a question.

DR. BENOWITZ: It is a question I guess for Roche

or perhaps CDC. The fact that in some populations the resistance can be 67 percent, it is not clear to me at all how a practice of having a stockpile in the home would be adjustable in response to what particular virus is circulating at one time. So, having your kit for five years, it may work in some years and may not work in others. I just want some clarification on how this is going to work.

DR. McGUIRE: Sure. I would invite my colleague, Dr. Donald Low, to help you with that.

DR. LOW: Could I have R-61?

[Slide]

I think this is really an important concept to get on the table because I think it addresses the concern about resistance with a pandemic strain. What we have put on the table today is two terms that really aren't familiar to most of us. One is drug-induced resistance and the other is this naturally-occurring resistance.

Drug-induced resistance, as we have seen with antibiotics and bacteria, is something that occurs when you expose an organism to a drug such as oseltamivir. It develops resistance. It is not a very fit drug, a fit

organism, and we know that because we don't see it spread. In fact, prior to the 2006 season Tamiflu resistance was less than one percent in adults. So, it was not a very fit organism.

So, look on the right-hand side, naturally occurring resistance is something completely different. As we heard this morning, it is not related to drug use. In fact, what it is, is mutations that occur in other places in the enzyme and, as a result of loss of fitness, compensatory mutations are occurring and one of these happens to be a mutation that makes oseltamivir resistant.

So, this is a very rare event. We haven't seen it before. This is a thin organism. So, you are hearing about the fact that wee are seeing H1N1 resistant oseltamivir now in some places as high as 67 percent. So, why is that happening and should we worry about it with a pandemic? So, if I could have slide 59?

[Slide]

I know this is a difficult slide but I think for everybody it is worth just spending a few seconds on it because I think it really provides an important message. This was published in PLoS just a few months ago and it

looks at these resistant strains.

Looking on the left-hand side of this figure, what you see here, just looking at the height of the bars, that is a wild strain of H1N1 that is fit and it is fully susceptible to oseltamivir.

Now look in the middle and you see the bars have dropped down, and that is bad. Why have those bars dropped down? Why has the enzyme become modified? The reason is that the virus is adapting. It is shifting. It is undergoing antigenic shift in order to escape the immune system. You can tell that. Down here you will see the number of mutations which have taken place, which is allowing antigenic shift to occur but, notice, there is no mutation down here at that hot spot that we have all been talking about this morning.

Now, in the far right you see that the virus has regained some of its fitness. The enzyme is now more functional. But the way that it did that is by that mutation there which results in oseltamivir resistance.

So, this is not driven by drug, and the interesting thing is that if this neuraminidase continues to evolve and undergo antigenic shift as we expect it to, it

may well change again and it may well its benefit to get rid of that mutation at 275, or it has been referred to 274 but the proper nomenclature is 275. So, it could be that in a year or two I expect that we are going to see the H1N1 100 percent resistant to oseltamivir, maybe next year as well, but the following year it might disappear completely as this virus undergoes antigenic shift and it loses the value of having that mutation.

So, coming to pandemic influenza a new strain introduced into a population that hasn't seen humans, hasn't seen antiviral drugs, sure, there will be drug-induced resistance and we wouldn't expect it to be any greater than what we have seen with the prior history of using oseltamivir, one to four percent, maybe higher in children.

Will this happen? It is possible. But it is a rare event and it is one of those things that we just can't predict.

DR. McGOWAN: Tat is great, thank you. Maybe we could move on to Dr. Good who had a question.

DR. GOOD: Just a question about the compliance studies. I am just curious, realizing that there aren't a lot of patients in these studies and it may not be possible

to draw any firm conclusions, are you going to query the patients about prior receipt of influenza vaccines and whether or not they received the vaccines during the year that they received these neuraminidase inhibitors?

DR. McGUIRE: Yes.

DR. NG-CASHIN: Yes, we will too.

DR. McGOWAN: That was an easy answer. Dr. Shrank, you had a question?

DR. SHRANK: Thanks. This is for the Roche folks. There is lots of evidence to suggest that parents have a difficult time with the numerical challenges of dosing for their kids even for relatively simple and straightforward medications, and it seems like the challenge may be greater here in that somehow you have to figure out a proportion of a capsule. I wonder if you could just describe in sort of very clear terms what the parent's job will be, and how to actually do this.

DR. McGUIRE: Sure. Slide up, please.

[Slide]

This is actually contained in the MedKit booklet. What we would do is provide these directions to the parents in terms of mixing; what materials they would need to have

during this process. By the way, this is everything we will be testing during the mixing study to ensure it is being comprehended. Next.

[Slide]

So, what you have here is the steps. We tried to use diagrams to show it exactly; emptying the capsules, adding the media in which they would be giving the Tamiflu to the child. Next, please.

[Slide]

Then, what we have done is we have used the teaspoons to provide this to children. We are also looking into a dosing mechanism or tool, if you will, to be contained within the MedKit, other than the teaspoons. But we want to make sure that parents understand it this way in case that spoon or device that we put in there is lost as well and then they wouldn't have that. So, we will be testing this and that is what we will be providing to the parents.

DR. McGOWAN: Great. Dr. Parker?

DR. PARKER: Thank you. I am kind of a basic person and I appreciate so much that you included your mockups I guess of what some of the Tamiflu MedKit for

pandemic flu materials would look like. I am wondering if you could help us similarly with Relenza, making available to us the mockups at this time, and give a lot of comment related to the comprehension study for the label and the actual use. I think it would be so helpful if we could look at these materials, if you happen to also have the actual materials in your mockups that we could use as we begin to ponder what advice we can offer relating to the understanding comprehension studies for the label and the compliance. I think we can give you better information the more we are able to see.

The same thing with CDC with this guidance chart that I am very interested in that will relate to the ability for self-selection. As we provide insight, the more we are told about the task at hand and the more we can put our hands on it, I think we are able to offer you better information. So, if you have those available, maybe after lunch we could have them.

DR. McGOWAN: GSK?

DR. NG-CASHIN: I believe some visuals of the mockup are contained within the briefing document that was made available. We are still developing a lot of the

materials and it might not be as flushed out as it was for the Tamiflu MedKit that you are looking at, but we would certainly welcome talking about it a little more if you would like to.

DR. McGOWAN: Tim Uyeki?

DR. UYEKI: This is for both companies. Given that I think it is a reasonable assumption to expect local pandemic influenza activity to be about eight weeks, possibly, you know, plus or minus several weeks, and let's assume that use of these home MedKits is quite effective so you treat an index case used for prophylaxis, well, what about subsequent exposures in the community that occur after, say, that ten-day period and several weeks later one of the other family members comes in as an index case in the family? Would there be multiple MedKits used? Even if you assumed 100 percent effectiveness, this would be, like, for one exposure. So, I am wondering about the use of multiple MedKits.

DR. NG-CASHIN: At this point our development plan and what we have envisioned would only accommodate one way, if you will, so an index case within the house and then and/or prophylaxis of the household contact.

You are correct that should there be another index case that would trigger another course of prophylaxis and the MedKit, as we are currently envisioning it, wouldn't accommodate that.

DR. McGUIRE: With regards to the Tamiflu MedKit, right now, just to take a step back, that is why I think one of the mechanisms that will be important is some type of nonprescription OTC type mechanism that will allow availability if product were needed again quickly versus maybe what you have with prescription.

Our packaging is different and smaller. We have looked at potentially having a larger box, if you will, to hold multiple doses or more than just one course per family, and we will continue to review that.

DR. McGOWAN: Dr. Havens?

DR. HAVENS: First, will the HHS representatives be here in the afternoon for questions as well, or is this our only time to ask questions of the CDC and the HHS?

DR. COX: Yes, the HHS representatives will be available in the afternoon also.

DR. HAVENS: A preliminary question for the HHS representative before I get to the question for the

companies, do the benefits of the prophylaxis that are presented by the HHS come from what was referred to as the socially targeted model of prophylaxis, or do they pertain to what is being used here as the index case in the family model of prophylaxis? That is not clear to me. So, do the benefits suggested by HHS come from the model of prophylaxis that we are being asked to evaluate or only from the socially targeted model?

DR. McGOWAN: From HHS, whoever wants to take that question, come right ahead.

DR. SCHWARTZ: This is Ben Schwartz. The estimates from that model come from prophylaxis occurring among household contacts 24 hours after onset of illness in the index case in that household. It does not have anything to do with prophylaxis for other contacts in workplaces or in communities but only within the household.

That model also does not include the potential impacts of community mitigation or other strategies that would be implemented in a pandemic and also could have impacts on morbidity and mortality.

DR. HAVENS: Then the follow-up question to both companies is when you do the testing for your kits, you made

it clear there is a question about do you understand you are only supposed to use it for pandemic flu, but the algorithm actually is do you understand you are supposed to use it for pandemic flu in your own community and when there is a case in your family for prophylaxis. Are you asking that specific question to get at this issue of family-targeted prophylaxis versus if I go to work and there is a case there you are still not supposed to use it?

DR. NG-CASHIN: You know, the diagnostic algorithm that you are referring to is still under development. But as we envision it right now, trying to maximize the appropriate use, I think within that algorithm, besides making sure that people understand they only use it in a pandemic, is helping the consumer or patient differentiate between treatment for themselves as the point person or prophylaxis.

And, I think at this point we are thinking of household contacts, not contacts through interactions outside the home. But, that being said, that is what we envision at this point in time. We are in continuous conversation with CDC and HHS over the best way to construct that algorithm.

DR. McGUIRE: And to test the algorithm, obviously we will be testing it in the labeling and comprehension.

DR. McGOWAN: Great. At this point, I am very conscious that there are a lot of people who have questions to be asked. I suggest you jot them down. We will have a lot more time this afternoon set aside for discussion, but we do have a series of individuals representing various professional associations who have presentations to make and I think we should move to those before we break for lunch.

The first three individuals are actually joining us by teleconference. I believe the first person, I hope, who is on line is Brit Oiulfstad, from the National Association of County and City Health Officials. I would ask that these individuals, please, keep to your five minutes of allotted time as we have quite a few of you. Brit, are you there?

Presentations from Professional Associations

National association of County and City Health Officials

Home Stockpiling: Who Benefits?

DR. OIULFSTAD: Yes, I am. We have been having some technical difficulties on the phone so I hope that you will be able to hear okay. I would like to thank the

committee members for providing the opportunity to comment on the proposed stockpiling of MedKits for pandemic influenza.

Home stockpiling of antivirals is one of several mitigation response strategies for reducing morbidity and mortality during a pandemic although it may be less relevant than some other home-based strategies. While individual preparedness is something we all advocate, the National Association of County and City Health Officials, NACCHO, is concerned about the equity of access to antivirals and the numerous implications of individual home stockpiling. Presently there is no consensus among local health officials on individual home stockpiling.

NACCHO supports additional pharmaceutical, industry and federal government research on the utility and practicality of a MedKit approved by the FDA for individual home stockpiling of antivirals. Additional research and evidence would provide an informed platform on which NACCHO could support or reject the public health policy on home stockpiling.

Currently, many local health departments do not have access to sufficient stockpiles for treating their

populations. About one-quarter of states now have reached the quota needed for treatment and also have amassed additional stockpiles for prophylaxis for public health and critical infrastructure workers. However, another quarter of the states have purchased less than 50 percent of their treatment quota. Stockpiles available for pandemic vary widely from state to state.

Uniform access should be ensured through the established public health system. Individuals who live in states without adequate resources should not be penalized by having to purchase their own MedKits. Local health departments are improving on their ability to distribute medical countermeasures to individuals within 48 hours.

The federal government is not purchasing antivirals for 100 percent of the population, as is the case with other medical countermeasures, such as those for smallpox and anthrax. The federal government expects states to ensure an antiviral stockpile for 25 percent of the state's population. At this time not all states have reached this target and are unlikely to do so in the near future due to financial constraints, lack of political will and a lack of consensus on perceived benefit.

Moreover, it is not certain that the proposed antiviral MedKit will even be effective in a pandemic influenza. Recent global viral surveillance studies indicate trends towards resistant influenza A viruses. Viruses, by their very nature, mutate and the emergence of naturally occurring resistance to Tamiflu needs to be greatly considered.

Given that Tamiflu only shortens the duration of illness by 1.5 days, it should not be considered a silver bullet. We also need to consider the high cost and limited shelf-life due to state pharm. laws. The effect of long-term usage well over seven days has not been evaluated.

We need to keep in mind that prophylaxis is the entire duration of exposure and a pandemic will last for several weeks or months. An additional complication is the asymptomatic shedding that can be associated with influenza. Studies that support the effectiveness of antivirals when used as prophylaxis have been limited to a relatively restrictive and closely monitored environment.

It is unknown whether the antiviral effectiveness in these studies can be generalized to a pandemic. There is insufficient human data to evaluate risk of Tamiflu to

pregnant women, the developing fetuses, those who have hepatic impairment, nursing mothers, pediatric patients younger than one year of age.

There also needs to be further evaluation of the contribution of Tamiflu on pediatric patients with influenza who experience neurological events, some with fatal outcomes recently in Japan.

In addition, the proposal of offering these antivirals over-the-counter in essence relinquishes the role of the physician and places the onus for diagnosing cases, effectiveness of treatment and reporting of adverse events on untrained citizens, businesses and employees.

MMWR, January 25, >08, reports that even many primary care physicians do not correctly prescribe antivirals. Amantadine and rimantadine which are normally recommended for use lead to viral resistance, a recommendation starting in 2006, were prescribed by 26 percent of primary care physicians in the >06->07 season.

If medical professionals are remiss in their ability to keep current on recommendations, how can we expect the average American to utilize antivirals appropriately despite packaging of, quote, do not use until

a pandemic is declared, unquote?

No empirical studies have demonstrate the public's ability to effectively maintain a pharmaceutical, self-diagnose and self-treat for pandemic illness.

Since the effectiveness of this strategy is questionable at best and, given that these issues regarding antibiotic and antiviral resistance are emerging almost daily, the proposal to privately stockpile a pharmaceutical is not a position that is in the best interest of public health. It can be a waste of resources that could be better spent on other non-preparedness activities.

Emergency preparedness requires the public's trust. Public health recommendations need to be science-based and realistic. Recommendations need to be made with the collaborative agreement of expert and public health, infectious disease and medical practitioners for the benefit for the larger public. Thank you for your time.

DR. McGOWAN: The next speaker is Dr. Doug Campos-Outcalt, from the American Academy of Family Physicians. Doug?

American Academy of Family Physicians

AAFP Viewpoint

DR. CAMPOS-OUTCALT: Hi. Can you hear me okay?

DR. McGOWAN: Yes, perfectly.

DR. CAMPOS-OUTCALT: Good. Are my slides up, slide number 1?

[Slide]

DR. McGOWAN:: Yes, it is up.

DR. CAMPOS-OUTCALT: Good, and as I proceed down the slides I will give the numbers. My name is Doug Campos-Outcalt. I am the scientific advisor to the American Academy of Family Physicians. I am also at the University of Arizona College of Medicine, Phoenix campus. Thank you for inviting us to speak today.

[Slide]

Going on to slide number 2, the American Academy of Family Physicians agrees with the FDA assessment that the proposed storage and use of antiviral home kits has many similarities with over-the-counter medication use. Now, I would like to emphasize we are not advocating that it be made over-the-counter; we are just saying that there are going to be some similarities in reality if they are approved for home kit use or for home stockpiling.

Widespread stockpiling of antiviral medications

for future use at some uncertain time and under uncertain circumstances will lead to frequent medication use without direction and oversight by a trained healthcare professional. Therefore, we think the threshold for safety and types of studies regarding patient understanding and medication use should be similar to that for OTC medications.

[Slide]

Slide number 3. Family physicians are really the front line along with other primary care physicians in the nation's healthcare system and the public health infrastructure. It is really important to have collaboration between primary care physicians and local health departments and the national department of health. Now, in the event of a pandemic this kind of cooperation will be essential to minimize community-wide morbidity and mortality.

[Slide]

Going on to slide number 4, our concerns really are divided into two areas. One area, based on the information we were given, apparently lies outside of FDA considerations but I just want to mention a few points, and

that is the number of areas within FDA consideration that I want to address.

[Slide]

The fifth slide, areas outside FDA consideration, which other people have mentioned, have to do with equity and availability, distribution and financial coverage for home kits. I think we have serious questions about whether insurance companies will cover the price of a home kit for home stockpiling and some uncertainties in the future.

The second concern has to do with potential requests for prescriptions that come from patients for other than intended purposes, for instance, requests for prescriptions for relatives and other people who they might want to share the medication with, as well as after inappropriate use. What is a family physician to do if you prescribe for a home kit and a patient comes back six to 12 months later and says to you that they used it for seasonal influenza or other viral infection and now needs a refill?

[Slide]

Next slide. Physician time and effort needed to discuss home kits will detract from needed chronic care and other effective preventive care. And, we think that there

is a potential for physician liability for adverse outcomes that might occur with home kit use years after the medication was prescribed.

[Slide]

So, moving on in slide 7 to areas that we think are under FDA consideration currently, we think there are a number of questions that should be answered before approval is given for home kit storage. The first one is will patients properly store and then find the medication years after it has been prescribed and purchased?

The second, will patients recall instructions for use of the medication years after they have been provided? Will they be able to find those instruction materials that come with the medication as well?

The third question, will patients use the medication inappropriately for other viral and/or bacterial infections?

[Slide]

Moving on to slide 8, will the medication be used at the recommended dose and duration by all age groups?

Next question, how will changing dose requirements for growing children be considered and, you know, how will

that be handled?

Next question, will inappropriate use lead to antiviral drug resistance?

The next question on this slide, what will be the incidence of adverse drug reactions from home kit use, and how will these events be tracked? I would also like to echo the concern of the former speaker regarding its potential adverse consequences during pregnancy.

[Slide]

Next slide. Will patients understand the difference between post-exposure prophylaxis and chemo prevention, which is to use the medication to prevent infection in those at risk of exposure but not necessarily exposed?

Does post-exposure prophylaxis prevent infection or improve outcomes if one is infected? If so, among what age groups and risk groups?

Next question, can individuals accurately assess when they have been exposed to influenza?

[Slide]

Slide 10, does chemo prevention prevent infection or improve outcomes if one is infected? Who should take it,

when should they start, and how long should they take it for?

Next question, if the medication is recommended for chemo prevention only for those in high risk jobs, will other members of the public adhere to this recommendation? We think this has a lot of implications for proper use of the medicine if there is a limited supply.

[Slide]

Next slide, which is slide 11, how will patients know to request a five-day, which is the treatment home kit, versus a ten-day, which is a post-exposure prophylaxis home kit? Will they know the difference between these? Will they request both?

The second question on this slide, what measures will be taken if viral resistance develops and the home kits are no longer recommended? We anticipate that at that point there will be home kits spread around the community and what will happen because of that.

The last question on this slide, will use of the home kits continue to occur after a recommendation to stop using them has been given?

[Slide]

Slide number 12, and this I think kind of summarizes our position. Will the use of antivirals lead to a false sense of security and less adherence to other recommended measures such as social distancing, respiratory hygiene, hand washing, immunization against seasonal influenza or against pandemic influenza should a vaccine be available, and the use of face masks?

It may very well be that these measures will be as, or more, effective than self-diagnosing and use of home MedKits, and if these measures are not taken because people have a false sense of security the overall harms may actually exceed the benefits. And, that is our final question, which is will the overall benefits exceed the harms under this plan?

[Slide]

So, in conclusion, I want to thank you for the opportunity to raise these issues. We hope that they are considered seriously and we do want to work cooperatively with the HHS in developing effective response capabilities to pandemic flu. If there are any questions for me, I don't know when those are going to be asked but I do have a conflict and I am going to have to move on pretty soon.

Thank you very much.

DR. McGOWAN: Thanks very much, Doug. We actually have a list of other organizations who need to make presentations. I suspect we will be discussing many of your questions this afternoon and, obviously, that will be captured in the minutes of the meeting. So, thank you for joining us.

The final online participant is Litjen Tan, from the American Medical Association. Litjen?

American Medical Association

AMA Perspective on Use of Influenza Antiviral MedKit During a Pandemic Influenza Outbreak

DR. TAN: Thank you for the opportunity. Can you all hear me?

DR. McGOWAN: Yes.

DR. TAN: Good, thanks. My name is L.J. Tan. I am Director of Medicine and Public Health here, at the American Medical Association, and the AMA appreciates this opportunity to comment specifically on influenza and antiviral MedKits and home stockpiling of these MedKits.

I am going to present our views in actually two ways. I am going to present our views with respect to its

use in pandemic influenza and then its use for seasonal influenza as that was one of the issues that was brought up as something that you might all be talking about if time permits.

I, obviously, appreciate being the third speaker following NACCHO and AAFP and Doug actually captured a lot of the details that we would be sharing some of concerns with AAFP on. So, for that purpose I am just going to go ahead and just quickly go through my statement and try to save you some time.

For the purpose of pandemic planning the aim is always to support the need for, obviously, proper planning and preparedness for any kind of pandemic influenza. We also feel that timely provision of antiviral therapy, you know, either for treatment or for prophylaxis is going to be an essential part of the overall planning process and preparedness process.

But the AMA has not in general ever supported the concept of long-term individual stockpiling of pharmaceuticals, and we also have concerns about the use of a MedKit for individual home stockpiling of influenza antivirals for pandemic influenza. These concernsB-you

know, I will probably reiterate some of the things that have already been said earlierB-include the fact that we are concerned about long-term stockpiling in the face of an uncertain pandemic.

And, when we say uncertain we don't mean whether or not it is going to occur; we believe that is going to happen. It is just there will be uncertainty regarding the time when it occurs, the severity, etc., might actually increase the potential for misuse of the MedKits. For example, it is possible that the MedKit will be used by the public for seasonal influenza even though it is intended to be used only during a pandemic, and this could very well occur in the absence of an influenza diagnosis and appropriate counseling by a physician.

It could potentially lead to survival of resistant seasonal influenza strains and/or to an increase in adverse events. Additionally, inappropriate use during seasonal influenza, for example treatment of a cold, would also lead to decreased confidence in the public with regard to the effectiveness of the antivirals and this, obviously, could have ramifications for actual use during pandemic influenza. In fact, as we know, this is one of the most cited reasons

why people don't seek influenza vaccination; it is the belief that the vaccine doesn't work.

We also believe that long-term stockpiling increases the risk of improper storage and handling of the MedKit or unavailability when needed. For example, should the MedKit be improperly stored and handled its effectiveness will be compromised. There is also concern as to whether the MedKit can be recovered after it has been stored for a long time in somebody's cabinet, in somebody's basement and, if it is recovered, whether the contents would be used accurately. So, we would obviously like to get some information about that.

Finally, you know, with the mobility of the American population, we would also be concerned whether immediate access to the stockpile MedKit can be guarantied. Are people going to be away from their homes? Are they going to be on vacations? Are they going to be visiting people? And if that is the case, when the decision to use the MedKits is rendered, how would that be handled?

Then, long-term stockpiling also raises the question of appropriate communications to, and then appropriate use by the public when the MedKit is finally

used. For example, you know, in the long-term stockpiling kit duration will new data on resistance actually render the MedKit useless? If that is the case, how do we communicate that? All those new data result in new dosing requirements for example in children?

You know, influenza antivirals, specifically the neuraminidase inhibitors, are prescription products and they currently do not have the many years of post-approval use and experience to guide these decision-making processes.

Finally, although this is beyond the scope of your discussion today, as we were informed, the AMA does have some concerns that have been raised also earlier about equity of access to the MedKit; the potential that physicians and other healthcare professionals would face pressure to replace these kits should it be lost, should it be used inappropriately, etc.; and then also the potential for liability should an adverse event occur when using a MedKit years after it has been issued.

So, in summary, the AMA believes that public health preparation, which is the rationale for development of an influenza antiviral MedKit, could be achieved through other methods and we, obviously, remain very open to

discussing with the HHS some of the other methods including, for example, a formal plan for pre-positioning the antiviral medications in coordination with its distribution to multiple public and private networks that already exist.

Finally, some quick comments on seasonal influenza, we also question the need for influenza antiviral MedKits for annual seasonal influenza. We believe the use of antiviral therapy during seasonal influenza should primarily occur after the diagnosis of influenza and, of course, you know, in the best-case scenario confirmed with a rapid test then, obviously, after a discussion between the physician and the patient, and then a prescription for the antiviral medication has been issued.

In this circumstance the MedKit simply becomes a matter of product packaging and potentially providing a simpler, more understandable manner for a patient to start influenza antiviral therapy.

The AMA strongly believes that having a MedKit stockpile available for seasonal influenza would undermine the fundamental tenet of influenza prevention, and that is protection against infection through vaccination and other infection control techniques such as proper hand hygiene.

We really appreciate this opportunity to highlight some of these concerns with the concept of home stockpiling of an influenza antiviral MedKit and, obviously, we remain open to working and answering questions from the HHS and from the FDA committees on this issue. Again, thank you very much for this opportunity.

DR. McGOWAN: Thank you. The next individual is Dr. Luciana Borio, from the IDSA.

Infectious Diseases Society of America

IDSA Comments Regarding the Antiviral MedKits Proposal

DR. BORIO: Thank you for the opportunity to be here today. Good morning. My name is Luciana Borio. I am an infectious diseases physician and an assistant professor of medicine at Johns Hopkins University. I am also a senior associate at the Center for Biosecurity of the University of Pittsburgh Medical Center, and I serve as a member of the National and Global Public Health Committee of the IDSA.

IDSA represents over 8,000 ID physicians and scientists devoted to patient care, education, research and public health, and we are vitally interested in evidence-based effective means to reduce the transmission of infectious diseases, including pandemic influenza.

IDSA acknowledges that there is unmet need for the provision of potentially life-saving medication to families in a timely fashion during an influenza pandemic. However, we have several concerns regarding individual stockpiling of antiviral drugs in advance of a pandemic.

We know that every policy carries potential risks and benefits, but this policy introduces an uncertain time lag between acquisition and drug taking and, therefore, introduces uncertainties regarding the risks and benefits, making this proposal very challenging to evaluate and an adequate science base is needed to inform this calculation. For example, to understand the benefits we need to have a much better understanding than we do now of the efficacy of influenza antivirals when it comes to treating cases of severe influenza, which is an important proxy for pandemic influenza. We don't know, for example, what is the correct dosing and duration for the treatment of severe influenza. We might only learn that information once a pandemic occurs.

With regard to the benefits of prophylaxis, it will be difficult for patients to assess the optimal time to initiate a prophylactic course, and this difficulty is magnified given the potential for multiple exposures over

the pandemic period, as was alluded to by Drs. Bass, Bradley and Uyeki.

One must also consider the opportunity costs of this policy. Is it wise for the government to promote family purchase of a therapeutic of uncertain benefit which might potentially be rendered ineffective due to changing susceptibility of influenza viruses, and which carries a limited shelf life?

And, it is important to recognize that this policy does not obviate the responsibilities of the public health sector to provide life-saving medications to the population unless it is well-known that the vast majority of the population has acquired the individual stockpiles way in advance, and we cannot really assure that.

We believe that other solutions can also promote rapid access for the treatment and promote family preparedness and resiliency. IDSA continues to support exploring other strategies to assure rapid access to influenza antivirals. We believe that these alternative strategies should be explored and validated in the setting of seasonal influenza.

In summary, we urge very careful consideration of

alternative policies that might have a more beneficial risk/benefit ratio. Thank you.

DR. McGOWAN: Thanks very much, Luciana. The next speaker is Dr. Henry Bernstein, from the American Academy of Pediatrics.

American Academy of Pediatrics

American Academy of Pediatrics' Perspective of Home Antiviral Drug Stockpiling

DR. BERNSTEIN: Thank you very much. My name is Hank Bernstein and I am a professor of pediatrics at Dartmouth Medical School, and also a member of the Committee on Infectious Diseases at the American Academy of Pediatrics.

[Slide]

I thank you for the opportunity for us to present the American Academy of Pediatric's perspective on home antiviral drug therapy. The American Academy of Pediatrics is an organization, nonprofit, of 60,000 individuals, many pediatric primary care and many pediatric medical specialists, as well as pediatric surgical specialists. We are dedicated to the health, safety and well-being of infants, children, adolescents and young adults.

I should point out the last bullet here, that any decisions for endorsement from the American Academy of Pediatrics require approval from the American Academy of Pediatrics Executive Committee and the Board of Directors.

[Slide]

The home stockpiling concept is an important one, but many details remain unresolved. Some of the primary issues that face children include creating demand for an untested approach. We are concerned about the risks versus benefits for the individuals, for their families, for their communities, as well as the society at large.

There also is an additional burden on families, not just economics but apparently health management and health decision-making. There is also an additional burden on physicians and other healthcare personnel. Someone needs to educate people about the use of these home kits, as well as how to manage their children in the face of a pandemic. There are also obvious public health implications.

[Slide]

There are also issues that are unique to children. We have heard a lot about medication errors that can happen with adults. Will they get magnified when we highlight the

differences in children? We first need to determine the proper dose and we already know that many of the doses that are needed really depend upon the weight of the child. We have also heard that there may be a possibility of an increased need for an increased dose in a novel pandemic strain.

We also know that younger children are not able to take pills and actually need liquid preparations. So, we need to be sure that there is an adequate amount of the liquid preparation for the children depending upon the doses that are recommended. Of course, when you start talking about liquids there is always something about mixing, something about pouring out and giving it to the children. So, this actually extends beyond knowing but moves into knowing how, and that can be really difficult for families when they are caring for their children in a stressful situation like a pandemic.

[Slide]

There are other safety issues such as the adverse events. We have heard about bronchospasm. We have heard about GI. We have also heard about neuropsychiatric issues. These need to be addressed.

We also know that under-dosing is possible, and if there is under-dosing that obviously can reduce therapeutic effectiveness. But we also know that it can play a role in the emergence of resistance.

[Slide]

There are other unresolved issues for children, such as the inappropriate use of the MedKit. We know that having something at home when their children are sick and they are looking for a cure, and they want things better, they are going to reach for that MedKit and, hopefully, they will at least know where it is. We would prefer they not use it during seasonal influenza but we can't be assured that they won't.

Also, during a pandemic flu they are going to use it just as they would for other respiratory illnesses that perhaps are not pandemic in nature, and they won't necessarily wait for the local community to identify a pandemic.

Of course, there is a difference between treatment and prophylaxis, and remember that adult learning theory, when you have a MedKit at home the adult learning period is that you need to be predisposed; then you need to be

enabled; and then you need to be reinforced. It is pretty hard for all three of those to happen when a pandemic has been declared in your local community.

[Slide]

There are also additional unresolved issues for children. A level of complexity exists around this issue and until these details are resolved we will need to explore the impact of allowing home stockpiling uptake. We know that if, in fact, cost becomes an issue we would address and be concerned about the inequity as far as distribution of home kits. We also want to know that there is availability either at home or in the local community through distribution sites or through local pharmacies as needed.

We also are concerned that children are the great transmitters so the issue of social distancing needs to be included as well. Lastly, we want there to be an adequate supply available, not just for treatment but there are many members and many families and extended families and if, in fact, prophylaxis is recommended it needs to be available for all the family members, the cousins, etc., that are living in that particular home.

[Slide]

We also need to extend the unresolved issues for children and extend them to the healthcare personnel that are caring for the children. There is no question that this is going to be an increased burden on many individuals. Also, I mentioned about the importance of awareness and education.

It is difficult for healthcare personnel to be able to educate families about using these things at home if they don't know and have all the information about using them, and know the knowledge and have the know-how.

There needs to be time for discussion with parents. And, how often does that discussion have to happen if someone has a home medical kit and they have it there? Does it need to happen every year? How does it get reinforced day in and day out?

We also need to know the dosing with changing recommendations. People need to have the know-how for adjusting the doses and using it only for pandemic flu. Many of our providers, we encourage and support the use of the medical home. This is a mobile society and people change providers. Hopefully, they will take their home medical kit with them, but then they need to establish a

relationship with a new medical home and the details need to be worked out for everyone.

[Slide]

So, a harmonized approach is something that is very important and really should and must include the uniqueness of children. We need to develop a research agenda to address these identified issues and examine the outcomes of home stockpiling for children.

We also need to make decisions after the development of an evidence base so it is difficult for us at the American Academy of Pediatrics to necessarily endorse this without having all the data and the evidence in front of us. Thank you very much.

DR. McGOWAN: Thanks very much. The next speaker is Cynthia Reilly, from the American Society of Health-System Pharmacists. Cynthia?

American Society of Health-System Pharmacists

Distribution of Antivirals for Pandemic Influenza: Public Health Impact and Research Recommendations

MS. REILLY: Good afternoon. My name is Cynthia Reilly and I am the Director of the Practice Development Division at the American Society of Health-System

Pharmacists. ASHP represents pharmacists who practice in health systems and hospitals. The society's more than 35,000 members include pharmacists and pharmacy technicians who practice in a variety of health systems, including inpatient, outpatient, home care and long-term care.

I appreciate the opportunity to present the views of ASHP on the evaluation and distribution of the antiviral MedKit, including the types of studies needed to assess past practices for distributing kit; the role of home stockpiling; and interfaces of home readiness with public health entities.

ASHP commends the FDA for exploring this topic, as well as the CDC's effort in studying approaches that either alone or in combination will ensure timely and effective distribution of antiviral medications. Our comment today will focus on whether home distribution of antivirals is appropriate, based on an assessment of an earlier CDC study of home stockpiling of antibiotics, considerations unique to antiviral medication, and our perspective on other distribution methods for which studies are planned or underway.

The proposed household stockpiling of

pharmaceuticals requires that several assumptions be true including that these drug products are easy to maintain and use; that they are affordable; and that this method of distribution is acceptable from a public health and medical perspective. However, these and other assumptions do not hold true for home stockpiling of antivirals.

Perceived increases in the availability of antiviral supplies to enhance production in the spring of 2006 have heightened interest in home stockpiling. The stockpile supply has slowly increased and it now nears the federal goal of 81 million antiviral courses, the estimated supply necessary if 25 percent of the population were to seek treatment.

However, this supply goal does not explicitly include the number of doses needed for prophylaxis or treatment courses during the extended time of at least six months that is projected for the development of a strain-specific vaccine.

Characteristics of the influenza strain will also affect which individuals need treatment or prophylaxis, for example, based on geographic location or patient age, as well as the dosage and length of therapy needed to ensure

effectiveness.

These factors may alter the current estimate of stockpile needs. A full assessment of these considerations will likely demonstrate that we do not have an abundance of antiviral drug supplies. Home stockpiling is not advised in the absence of sufficient courses for the priority groups that have been identified to receive antiviral treatment and prophylaxis, including patients admitted to hospitals, healthcare workers, emergency services personnel, and outpatients at highest risk.

Home stockpiling of antiviral MedKits has also been proposed on the positive findings of a recent CDC study of an antibiotic MedKit. That study demonstrated that, quote, participants appropriately followed instructions regarding storage and reserving the emergency MedKits for use until directed, end quote. However, these results may not be generalizable to antiviral MedKits because it may be more difficult to give explicit instructions to the public on when to initiate antivirals due to the gradual and regional spread of a pandemic and the generalized symptoms of influenza that hinder quick diagnosis.

Due to public fear, misinformation or mis-

communication, patients may use the MedKit antivirals for prophylaxis under circumstances when treatment is a priority for controlling a pandemic. This would exhaust antiviral supplies prematurely and inappropriately.

In their MedKit study summary, CDC recommends additional areas of study such as labeling comprehension and simulation studies. ASHP agrees that the areas identified in that report warrant further study for antibiotic and antiviral MedKits. While the extent of inappropriate use was limited in the earlier study, it is important to note that the study occurred under ideal circumstances in which carefully selected consumers received detailed instructions. With wider distribution it is unlikely that all prescribers will maintain the high level of counseling provided in the pilot study.

ASHP recommend a cohort study that provides variable counseling to each group as a method to better assess the extent of adherence to instructions that is likely to occur during actual use. The ability of different types of patients to appropriately understand and follow MedKit instructions should also be studied, especially among segments of the population with limited health literacy.

Finally, the proposed study should assess time intervals that extend beyond the two, four and eight months evaluated in the initial study.

Adherence to recommended product storage should also be assessed. It is well-known that extremes of heat, cold and moisture can render many medications ineffective. Without proper storage antiviral medications would not only be ineffective but they would also promote a sense of security that could result in behavior leading to increased spread of the disease.

To ensure equitable access barriers such as ability to pay and geographic variation and healthcare access should also be considered and addressed.

Home MedKits have been recommended as a mechanism to ensure timely access during a pandemic outbreak, circumstances when patients may be unable to gain timely access to their physician. While timely access is critical, I have just described how many patients may take the medications inappropriately. This concern is significant because widespread inappropriate use of antivirals will lead to resistance.

In early 2008 the World Health Organization

reported that resistance to oseltamivir in some United States and Canadian isolates had increased from previously reported ranges of under five percent to a range of five to six percent. While these estimates represent resistance in seasonal influenza isolates, the data does raise significant concerns about the use of existing antivirals in a pandemic outbreak and inappropriate use will heighten those concerns.

Nonprescription availability of antiviral medications has also been proposed. ASHP policy opposes nonprescription status for any medication for which the development of resistance is a concern, and the Society is opposed to nonprescription availability of MedKits or their components, be it community pharmacies or other retail settings. However, ASHP would support availability of these drug products without a prescription through mechanisms overseen by public health officials who would determine when and where the products are needed.

Other methods of distributing antivirals to the public in a timely manner have been proposed and tested, such as just-in-time packages tested through the city's readiness initiative where the U.S. Postal Service delivered packages to homes.

ASHP was pleased to learn of the CDC's October 2nd announcement about the launch of a second phase of the MedKit evaluation study that will assess the distribution of anthrax treatment via the United States Postal Service. This strategy has several advantages, including centralization of the stockpile to maintain control over where supplies are dispersed, and the ability to transfer limited supplies to affected areas.

The Society looks forward to evaluating the outcomes of that study and other components of the emergency MedKit evaluation study that will assess classic points of dispensing, pre-deployed community caches and first responder distribution.

In conclusion, ASHP strongly supports and encourages individual preparedness planning and recognizes the importance of an all-hazards approach to home readiness. However, the Society does not support the use of antiviral MedKits for home stockpiling at this time.

Our opposition is based on concerns about limited supply and antiviral resistance resulting from improper use, and this stance is consistent with at least nine state departments of health that have also advised against the use

of home antiviral stockpiles.

ASHP believes that personal responsibility for readiness should not include pre-acquisition of antiviral drug products. Efforts should, instead, focus on consumer knowledge of public health entities that will provide these treatments when needed. In the future home stockpiling of antiviral medications may warrant additional consideration if antiviral medication supplies improve, additional characteristics of the viral strain are known and, therefore, are better predicted, and better treatment options are available.

ASHP is interested in working with the FDA, the CDC and others to study alternative approaches to distribute, dispense and use antivirals, including best practices for educating the public about their critical role in these efforts.

Thank you for your timely consideration of ASHP's perspective on this important public health issue.

DR. McGOWAN: Thanks very much, Cynthia. The next speaker is Marcie Bough, from the American Pharmacists Association.

American Pharmacists Association

The American Pharmacists Associations's Comments on Stockpiling Pandemic Influenza MedKits

DR. BOUGH: All right, good afternoon. Thank you. Again, my name is Marcie Bough. I am a pharmacist with the American Pharmacists Association where I serve as Director of Federal Regulatory Affairs.

APhA is the first established and largest professional association for pharmacists and we represent over 63,000 pharmacist members, providing care in all different practice settings. I thank you for the opportunity to provide our comments today.

[Slide]

I have just one slide. I will go through these main topics and give you the role of what pharmacists should do in pandemic response, and go through our perspective on appropriate or inappropriate storage, expiration, disposal, economic cost and equal access.

Pharmacists are often considered the most accessible healthcare professionals, particularly in rural areas, inner cities and other under-served areas with limited access to primary care. As we demonstrated during hurricane Katrina and subsequent hurricane responses,

pharmacists serve a vital role in providing front line response for clinical services, assessment, education and dispensing of medications.

Pharmacists have also demonstrated a serious commitment to preventing disease through immunizations in a wide variety of practice settings. Currently, pharmacists are authorized to administer immunizations in 49 states and over 40,000 pharmacists have been trained and certified to administer immunizations.

From a public health perspective, pharmacists are prepared to serve as responders in event of an influenza pandemic, and to educate and dispense antiviral medications in collaboration with local, state and federal activities.

We recommend that the committees consider the following concerns related to home stockpiling of antiviral MedKits: We are concerned that home antiviral medication kits may not be used appropriately, as we have heard before today. Although the intended use may be to improve access, shorten the time to first dose and ease distribution burdens, an informed consumer will likely know that the same medication is also used for seasonal flu, thereby increasing the likelihood of inappropriate use for seasonal flu or

other viral infection. Such use may also lead losses and restocking of a home medication kit if it was used in appropriately with enough doses for a declared event.

In addition, the committees should consider how products' labeling directions, therapeutic algorithms, and packaging may influence use and self-care at home. Labeling needs to clearly state that it is only indicated for pandemic flu with no reference to just seasonal flue. Misuse and overuse of antivirals could also contribute to a supply shortage when needed for a national pandemic response and lead to the development of antiviral resistance.

Also like storage issues with any medication, we are concerned with the potential for inappropriate storage of at-home antiviral MedKits. In the context of a pandemic response, antivirals may have lengthy storage times, years maybe, in settings that have high temperature and humidity fluctuations, thus jeopardizing the integrity and potency of an antiviral medication.

In addition, home storage may not have adequate supply for first dose coverage or longer treatment protocols when needed in responding to pandemic response for an entire household. Maintaining storage at the pharmacy or using a

pharmacy as a distribution center for pandemic response would allow for a more controlled storage environment, access to healthcare providers and appropriate dosage information, and flexibility in the local supply stock to serve as either the local response or transfer to another location that is dealing with a pandemic.

Related to storage, we are concerned with the potential for home antiviral MedKits to be stored long enough to exceed their expiration dates, which could be by years. Home storage lacks the benefit of a rotating stock in a pharmacy where storage is in a more controlled environment and expiration dates are actively monitored.

Related to both storage and disposal, the healthcare system already struggles with appropriate disposal of medications, especially when trying to limit introducing drugs into the water supply. Similar to disposal information from FDA, APhA is a partner in the smart Rx disposal campaign, focused on appropriate medication disposal. We encourage the committees to consider the need for labeling information with regards to disposal, especially for large stockpiles that may go past their expiration date.

Regarding economic impact, we encourage a system that builds upon the current pharmacist, healthcare provider and distribution systems where use and storage issues can be managed and addressed. Pharmacists and pharmacies can serve to administer, screen, educate, refer and distribute medications as part of an integrated overall response process. However, any response will also need to address and consider sustainable business models and practices and address who is paying for these medications. Is it individuals, families and assistance programs versus the government or is it a combination, and in what purpose is the payment for? Is it in the purpose of preparedness stockpiling or is it the purpose of response and prophylaxis?

Finally, we are concerned that all patients need to have equal access to receiving antiviral medication kits, not just those that have the potential for insurance coverage or the means for cash payment. Payment voucher systems or other options will need to be considered to avoid creating groups of patients that may not have ready access to these medications or to the distribution facilities or systems at the time of a pandemic response.

We also encourage the committees to recognize the need for integrating pharmacist and pharmacy infrastructures into whatever system is developed for widespread distribution of pandemic antiviral medication kits, whether it is prescription only or versions of behind-the-counter or over-the-counter distribution.

We need to ensure that consumers have access to pharmacists and other healthcare providers to provide them with information for appropriate use of these medications that would be a supplement to the product labeling and treatment algorithms in the product packaging. Such activities should not be looked upon solely as the distribution of the commodity but, rather, as the healthcare interaction.

In closing, our concerns can be addressed by utilizing pharmacists as a resource to provide surveillance, assessment, early detection and referral, and education and instruction on pandemic response, and the appropriate use of those medications. Use of the pharmacy as a point of distribution for a local community when appropriate for a pandemic response is also something that pharmacists are willing to work with in collaboration with other healthcare

providers and, again, the local state and federal activities.

We look forward to working with the FDA, the manufacturers and other stakeholders to address these concerns that are raised here today as this initiative moves forward. Thank you for your time.

DR. McGOWAN: Thanks very much, Marcie. The final speaker in this section is James Blumenstock from the Association of State and Territorial Health Officials.

The Association of State and Territorial Health Officials

State and Public Health Agency Perspective on Pan Flu Antivirals MedKits

MR. BLUMENSTOCK: Thank you, Mr. Chair, and good afternoon. I certainly want to say thank you on behalf of the Association of State and Territorial Health Officials to be here this afternoon to address you on this very important and timely matter.

My name is Jim Blumenstock and I am Chief Program Officer for Public Health Practice for ASTHO. I think one of the advantages of being the closing presentation during the morning session is that it allows you to do two things. Number one, to reinforce some of the very important

messages that I believe you heard earlier today, and also to raise a few others that may not have been touched upon, which I think is very important during this deliberation.

For those of you who don't know, ASTHO, the Association of State and Territorial Health Officials, is a national association that represents the chief health officials of 57 state and territorial health agencies. We are committed to the formulation of sound national health policy and enhancing the practice of state-based public health.

As my colleague from NACCHO mentioned earlier, ASTHO as well does not have a formal position on home stockpiling of medical countermeasures. There is no strong or clear consensus in our ranks on this matter. In simplest terms, I believe the jury is still out in the minds of professional judgments of the state public health professionals.

To illustrate this point I want to raise or share with you reference to a recent letter sent to Secretary Leavitt and Rear Admiral Vanderwagen from the National Biodefense Science Board on the topic of home stockpiling of antibiotics for anthrax attacks.

While there really isn't any dispute over the main themes or messages in the subject letter, the imperative need for rapid distribution of countermeasures, the need to demonstrate the scientific and practical benefits associated with home stockpiling, risk quantification including misuse, inappropriate dosing, potential for adverse events and resistance, and really gaining the public confidence by avoiding confusing or conflicting messages on this issue, especially among those that are trusted agents in the community such as the healthcare and the public health practitioners.

That being said, our members have varied opinion on the degree of caution or reservation exhibited in this letter. Some believe it is right and on target, while others feel that it may be overly cautious and could stymie exploration and advancement of this alternative.

Nevertheless, I am confident and comfortable to stand before you today and share with you our general concerns and suggestions as you continue the necessary examination on this issue relative to the safety, efficacy, reliability, feasibility of and necessity for antiviral MedKits as a suitable medical countermeasure while still

being adequately protective of public health.

I want to start off by sort of giving you a quick line listing of our inventory of the pros and cons for antiviral MedKits. Many of these you have heard before.

The pros, as we see it, are that, number one, it does create opportunity for more courses of antivirals to be stockpiled and readily available. It prepositions medications in the home that could be beneficial for immediate treatment initiation upon symptom onset and, again as mentioned earlier, it does support the practice and principle of a community mitigation strategy of social distancing.

It could reduce the strain on public distribution modalities and possibly the healthcare system. It may increase the public sense of self-empowerment during a pandemic, and it could serve as one of a number of strategies in the overall response plan for medical countermeasures distribution.

On the other side of the coin are the cons. As you heard repeatedly, the potential for misuse, adverse events and increased resistance; access and cost considerations; and the potential for creating inequitable

distribution and availability of this countermeasure; an unclear level of acceptance by the public and healthcare community and, again, the challenges in factoring in this approach, in the overall planning for wide scale distribution to the public by the public health agencies.

So, in closing what I want to do is just sort of drill down to two categories of recommendations that we would like to share respectfully with the joint committee.

First, clearly to reinforce your plans to move forward with additional studies to better determine the actual value and utility of home stockpiling. The summary or the review of the three types of categories with regard to label comprehension, compliance, dosing administration studies, clearly we would support those.

One suggestion quite possibly, while there were several references to the St. Louis anthrax antibiotic test in St. Louis, another source of information may be the states that have nuclear generating stations. For a good number of years many of the public health agencies have, in fact, been putting home countermeasuresB-what comes to mind is a thyroid blocking agentB-in homes of citizens living in an emergency planning zone, initially ten miles and I

believe now it is extended to 20 miles.

Those are some fairly mature programs and activities and I would suggest to you that the states and possibly the FDA itself and the Nuclear Regulatory Commission may have a wealth of information from on-the-ground experiences as to really what has been learned; what is working and what isn't. At the very least, it may help to inform study design. It may also help you in your deliberations when you review the studies.

In this area, I would also like to suggest two other possible categories for further studies and research. In Dr. Tegeris' presentation he implied that home MedKits may, in fact, be a viable means to close the gap in the strategic plan for antivirals in the community. What I would suggest is possibly considering some type of a consumer interest or consumer acceptance study to really get an evidence base that would help inform and drive that significant planning assumptions. To me, that is sort of the threshold question on why we are going down this road in the first place.

The other category of research could possibly be post-approval. As I understand it from hearing the

presentations this morning, all the studies that are under plan would be pre-approval studies. Well, clearly, I would like to suggest that some post-approval longitudinal studies be considered to really evaluate, number one, if there is, in fact, any change in public acceptance, behavior and practice and any deterioration in the compliance information that was garnered to drive approval in the first place. So, I would respectfully suggest that as being considered and deliberated by the group.

The last category of recommendations, which was also mentioned several times before, is really that the home MedKit clearance must be considered in the context of the other feasible dispensing modalities, and really recognizes its inter-dependence with public policy and tactical considerations regarding sale and distribution, percent population to be served and benefitted and, of course, how to handle the consequences associated with misuse and adverse event investigation, and clearly to ensure that it is integrated in the overall state pharmaceutical countermeasure management and distribution plan.

Again, quite often today the discussion was that it would be the local or state health official that would

give advice to the public as to when to start consuming the home MedKit. Clearly, public health and the practitioners need to be fully involved and supportive of this activity, and knowledgeable. I think we could predict that while the manufacturers will clearly provide significant support to the consumers, public health as well as community healthcare providers will, in fact, be turned to, to provide significant complementary customer support, whether it be during the event or months or years out of the event, for people who would venture to purchase these items.

Clearly, there is a recognition that there will be special needs and at-risk populations that will really need community-based support and assistance to understand the proper management and to comply with the storage requirements and truly understand when orders are given or directives how best to apply.

So, again, I wanted to share those last three points really to reinforce the importance and value of state and local public health in this initiative, and to ensure that they clearly are part of the planning process.

In closing, again, I appreciate the opportunity to present our thoughts and concerns to you. We stand ready to

support the FDA and the advisory committee with regards to your deliberations and whatever operational aspects you would like to hear from us. So, again, thank you very much.

DR. McGOWAN: Thank you. That concludes all the presentations for this morning. We are going to break for lunch now and we will reconvene at 1:45. I would once again just remind the panel members that you should feel free to discuss anything apart from the contents of this morning. Thank you.

[Whereupon, at 12:45 p.m., the proceedings were recessed for lunch, to reconvene at 1:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. McGOWAN: We will now move to the public hearing session of today's activities. As of this morning, no one had actually signed up for this session but I have chosen to allow Ben Schwartz, from HHS, to walk us through the algorithm for pandemic flu.

Before he begins that, I just have the obligation to read a statement about the open public hearing session: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the contents of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and the committee in the consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

I will now turn to our only speaker for this session, Ben Schwartz, from HHS.

Open Public Hearing

DR. SCHWARTZ: Thank you very much. I appreciate the committee allowing me to make this brief presentation.

This morning we heard a number of questions from members of the committee about the diagnostic algorithm. We heard it referred to by both the manufacturers and then there were questions that were asked by the committee.

The issue of can people use these products safely and effectively also was raised in the comments from the medical societies. So, by sharing this diagnostic algorithm with you, hopefully, it will answer many of these questions you have.

I am going to just briefly describe the rationale for putting together an algorithm. Part of the rationale is related to MedKits which we are talking about today, but also partially it is related to the potential need to have the ability to develop telephone triage systems in a pandemic in order to reduce the burden on healthcare providers.

So, by having an algorithm through which influenza can be diagnosed safely and effectively we then have the ability to facilitate those triage systems, as well as to provide for appropriate use of these home stockpiles. So, the goal is that we want to facilitate timely, safe and effective antiviral drug use.

The process of developing this MedKit includes the formation of a working group, and that working group has representatives from the American Academy of Pediatrics, the American Academy of Family Physicians, the AMA and IDSA, and all of those organizations spoke this morning, as well as representation from the CDC Influenza Division. The process included a literature review, focusing specifically on the diagnosis of influenza as well as on risk factors for hospitalization and death.

We had a number of conference calls where we developed and modified the draft algorithm. Let me be very clear, we did not vet this algorithm scientifically with the manufacturers but, rather, we talked with them, given their communications expertise and the need to be able to communicate the algorithm in the package insert.

So, they gave us input about those communications issues but the algorithm itself, as we have designed it, is based on the opinion of this medical group and was not affected by the consultation with the manufacturers. Then, the step that has not yet occurred is the official review by participating medical societies.

The priorities in formulating this algorithm are,

first, to maintain patient safety and we do this in a number of different ways, first by referring persons who have danger signs of very severe illness for emergency care. We also, through this algorithm, refer persons with signs of serious illness or who have risk factors for rapid progression to serious illness either to contact their healthcare provider or an emergency room.

We recommend periodic reassessment of people who do not meet influenza diagnostic criteria if at the point in time that you are evaluated you don't meet those criteria, then you get reassessed periodically. Finally, we recommend either emergency or routine medical follow-up as appropriate for those who don't improve or develop signs of severe illness.

The other priority in formulating the algorithm was to achieve sensitivity in influenza diagnosis while, at the same time, maintaining reasonable positive predictive value.

John Tegeris showed this slide earlier, and this is the basic outline of what the algorithm includes. So, the first component is whether the health department has announced local circulation of pandemic flu. If not, then

the algorithm would not apply and one would not use their MedKit. If there is local circulation of pandemic flu and somebody has any signs of a febrile or respiratory illness the first question is whether there are signs of severe illness, danger signs, in which case one would call 911 or go to an emergency room.

If not, the second component is whether there are signs of serious illness requiring medical consultation or high risk underlying conditions, in which case one would contact their healthcare provider.

If not, then one would proceed through diagnosis for influenza and start antiviral treatment if the diagnostic criteria were met. If those criteria were not present one would take symptomatic therapy while reassessing every 6-12 hours. And, if antiviral drugs are needed there would be recommendations for when medical follow-up is needed.

So, let me fill in those blue boxes with some of the specifics. So, what are the danger signs? These are danger signs for people who may have pandemic influenza, but also for people who may have other serious illnesses and incidentally have fever or respiratory symptoms. So, they

include the inability to talk or, for instance, to feed due to breathlessness, evidence of cyanosis, chest pain or being unresponsive or incoherent.

If one does not have those danger signs, then you move down to the next blue box which is serious illness or risk factors for serious illness. And, the signs of serious illness include shortness of breath, severe vomiting, concern that medical assessment is needed, or less awake or not recognizing family and friends.

Or, if the ill person belongs to a high risk group, that also would be reason to contact a healthcare provider, and that could be because of a medical condition affecting immunity, because of a medical care visit during the past six months for an underlying disease like heart disease, lung disease, kidney or liver, or diabetes, or if one is very young, less than age two, or great than or equal to 70 years old.

There have been studies published by Elko Hauk[ph] in the Journal of Infectious Disease and in other medical journals which have identified these risk factors for hospitalization and for mortality. So, the reason why these are highlighted is people who have these factors are more

likely to progress to severe disease and may benefit by contacting their healthcare provider rather than just taking an antiviral drug on their own without any medical consultation.

So, now we move to the signs that are diagnostic for influenza. For persons five years old or greater the diagnostic criteria are fever greater than 38 degrees centigrade plus cough during the last 12 hours. For children who are between 2-4 years old, fever greater than 38 degrees centigrade plus either cough, runny nose or congestion. The reason why the respiratory symptoms are broadened in young children is that they may not as frequently experience cough.

Finally, the last blue box on the algorithm is recommendations for follow up. There are two different categories in terms of follow-up recommendations. One is if danger signs are present the recommendation would be to go to an emergency room or call 911, whereas, if there were continued fever, severe vomiting or sings of dehydration, or worsening, or inability to care for an underlying medical condition the recommendation would be to contact a healthcare provider or go to the emergency room.

So, those are the specific components that are included in this draft diagnostic algorithm. Now, the algorithm also includes a page of instructions for patients and families.

So, one of the issues that was talked about this morning the dosing regimen. What if it is different in a pandemic than for routine influenza? So, the recommendation is that there should be a hotline and/or website to confirm that these are the appropriate recommendations for treatment and prophylaxis.

In addition, it was raised, what if one's underlying medical conditions change? So, there is an instruction to contact the healthcare provider if medical conditions have changed since being prescribed the antiviral drugs, for example, presence of a contraindication, pregnancy, renal impairment with oseltamivir. Then, there is also guidance included in this algorithm to reduce the spread to family members and to the community such as in the household having a sickroom and a single caregiver, and emphasizing the community mitigation recommendations for isolation, quarantine and social distancing.

Finally, there is guidance provided on household

post-exposure prophylaxis, including dosing regimens, precautions, contraindications and guidance for switching to treatment if symptoms develop.

Now, one thing that was discussed this morning is whether one would start taking prophylaxis if there were an exposure in the community or the workplace. I would point out that this refers specifically to household members of someone who is diagnosed as having influenza.

Finally, the algorithm includes guidance on what to do if a side effect occurs in terms of contacting a healthcare provider or seeking emergency care, as well as reporting to the FDA MedWatch system.

So, I appreciate the opportunity to share this. Let me emphasize that this is still a draft algorithm. It has been developed in conjunction with the medical societies but those societies have not offered their official endorsement at this time.

DR. McGOWAN: Thanks very much, Ben. Would you be amenable to taking a few questions from the panel?

DR. SCHWARTZ: Sure.

DR. McGOWAN: There is a question on my right.

DR. BRASS: Yes, you mentioned that the algorithm

was set up with respect to trying to achieve high sensitivity and good positive predictive value, which is obviously critical and important for making an assessment of the relative risk to benefit and population impact of the diagnostic algorithm.

So, my question is what sensitivity was projected, what positive predictive value was projected, and whether it has been thought of validating that in the context of the seasonal flu season to see whether or not you can meet your objectives and whether this algorithm could actually be used without supervision?

DR. SCHWARTZ: Yes, it is a superb question. There are a number of publications, in particular the prophylaxis studies that Fred Hayden mentioned earlier but other studies as well, that have looked at the sensitivity, specificity and the predictive values of different individual and combination criteria.

One of the limitations of those studies is that many of them have narrow inclusion criteria at the very beginning so you are kind of stacking the deck in favor of increased sensitivity. So, a caveat is that we really don't know what the sensitivity would be if people applied this

when they developed signs of illness at home rather than coming to a healthcare provider and completing a screening questionnaire, if you will.

But in the publications the data suggest that signs such as fever and cough are present in perhaps 80 percent or so of individuals with influenza and the studies uniformly, very, very consistently, show that the combination of fever and cough does have a positive predictive value that is increased significantly higher. What is it? I can't recall the exact number.

DR. BRASS: I mean, obviously it will depend on what the background incidence of the illness is, and that is why you say in the context of some anchor. It would just give us some idea what the utility might actually be.

DR. SCHWARTZ: Yes, I think I need to go back to the studies. I don't want to give you a wrong number here.

DR. McGOWAN: Dr. Griffin?

DR. GRIFFIN: Yes, it looks really promising and I am wondering if there are plans to test the algorithm along with these other studies of compliance. Is there any way to test this algorithm?

DR. SCHWARTZ: I think it would be great to test it

clinically. I think that would offer some additional information to us about whether this is a sensitive and a reasonable approach to diagnosing influenza.

I do think, however at the same time, that we have to recognize how doctors are currently diagnosing influenza. I think you could ask some of the practitioners that are on this committee and I think that it is fairly consistent with what people do in a clinical setting as well. I don't know if anyone has any comments on that.

So, actually testing this in a clinical situation would be great, but I guess what I am saying is that I think this is pretty consistent already with what routine clinical practice is in the absence of a diagnostic test.

DR. McGOWAN:: Dr. Glesby?

DR. GLESBY: No.

DR. HAVENS: Thank you, my initial question was concerning the positive predictive value. It sounds as if we have no information on that. Just to point out, someone with a sore throat with a temperature of 100.4 and a cough of less than 24 hours duration would be told to take therapy. It is very sensitive, I am sure, but its specificity, it sounds like, would be dramatically

challenged.

One of the issues that you brought up though is to suggest that the CDC recognizes that dosing recommendations may change for a pandemic strain, and that a telephone number and a website would be available in the MedKit to give you a place to go to make sure that the dosing recommendations had not changed between the time the kit was produced and when you wanted to take it. Do I misunderstand what you said?

DR. SCHWARTZ: No, you don't misunderstand, and recognize that I am not making any predictions about how likely it is that the dosing or the duration would change. All I am doing is recognizing that some of the animal studies that have been done with H5N1 have suggested that a different dose or a longer duration may be preferable. So, if that situation ensued, I am saying that the algorithm would appropriately deal with that.

DR. HAVENS: Thank you.

DR. McGOWAN: Dr. Bradley?

DR. BRADLEY: Ben, I want to congratulate you for having the professional societies so involved in putting these algorithms together. One thing that needs to be

stressed is that pandemic influenza isn't your usual seasonal influenza and if the mortality rate is as high as 60 percent you want to test that sensitivity. It would be great to have it specific but that is the dilemma, to find the balance. In children, young children all you need is fever. You don't even need to have cough. So, if fever and cough or respiratory symptoms aren't there you are missing a group of children that you could potentially get early therapy to.

So, all of this I think needs to be cast in the framework of a very high mortality strain, even though the strain that eventually comes out might not have a 30-60 percent mortality. We just don't know.

In terms of increasing your sensitivity and specificity, I know that there is a lot of work on home kits to diagnose H5. So, if it turns out that it is the H5 type that becomes the pandemic strain there is a possibility that at some point in the not too distant future the FDA may have a diagnostic kit so that that answers your question. You would need to test and if it is positive you would treat.

DR. SCHWARTZ: Let me just, if I could, say one thing about the specificity, and this also relates to what

was said earlier today, and that is that if you diagnose someone as having influenza who really doesn't, recognizing that the specificity is not perfect, they will use the MedKit and will not have it at home then should they get influenza later in the pandemic.

But I would point out that this is all within the context of public sector stockpiling for treatment, and the goal of this public sector stockpiling is to provide enough antiviral drug to be available to treat everybody who needs treatment. So, if one uses their MedKit and develops illness later in the pandemic the objective, HHS' objective and the states' objective is that there is public sector supply to provide that treatment. What the MedKits would do, what the home stockpiling would do is just make that public sector supply go a little bit further.

DR. McGOWAN: I think we will take one last question that was from Dr. Day. Then we will have further opportunity during discussion of the questions, I am sure, to answer and address other issues.

DR. DAY: Concerning whether consumers can understand this or any algorithm, the ease with which they can do that depends upon the number of factors; whether

there are Aands @ or Aor's@, and so on, and the buildup of all of that.

So, an expression of that for whatever the final algorithm is can be made, and I would suggest that there is a database that could be looked at in comparison and that is from the Nonprescription Drug Advisory Committee. All those Rx to OTC switch applications could be consumers make self-selection decisions, and what was the comprehension rate on that, and you could get some kind of idea based on how complex this algorithm is relative to those. Say, for example for statins it was very difficult for people to make that decision.

DR. SCHWARTZ: Thank you. I have actually learned a lot from the manufacturers trying to figure out how they can communicate this in a simple way because, as you can see, there are a number of steps. So, that is a good suggestion.

DR. McGOWAN: Thank you, Ben. I just need to let you know that the open public hearing portion of this meeting is concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the committee, as well as

the public comments. So, I would now like to pass over to Dr. Birnkrant who will proceed with the charge to the committee.

Charge to the Committee

DR. BIRNKRANT: Thank you. I will be brief due to the numbers of questions and the time constraints that we face.

I wanted to thank everyone for their presentations this morning. I thought they were quite helpful. The presentations, however, and the follow-up questions raise new issues for us that we will need to consider both today and in the future.

This morning we spoke extensively about the concept of a MedKit and the development pathway, including suggestions and opinions on how the concept and product can be tested. If you agree that the concept is a good idea, which is the basis of the first question, then we will need to focus on how to make it work, which is the subject of the remaining questions.

We recognize, however, that not all issues can be answered in a one-day meeting on a complex topic such as MedKits for influenza. We are looking to you for an

interesting discussion, a discussion that forms the basis for future interactions. Thank you.

Advisory Committee Discussion

DR. McGOWAN: Thanks, Debra. We will now begin the panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

Before I begin by reading the first question, just as a reminder to the committee, or committees, this is a very large group and, as I said earlier today, it would be great if people could ask very precise, focused questions and if those wishing to respond could do so in a similar fashion and we can probably try and get through all of these questions.

The first question, please comment on the concept of a prescription influenza antiviral MedKit intended for use during a pandemic. Specifically address potential risks and benefits for individual consumers and the U.S. population if prescription MedKits were approved with the intention of home stockpiling. Perhaps we can begin with Dr. Brass.

DR. BRASS: I first began with kind of a large

picture frame when I thought about this question. This is a situation where the public benefit is potentially very large. So, restricting access based on relatively minor or theoretical concerns would be undesirable. But, by the same token, the availability without ensuring maximal efficacy and safety would not be useful or not optimal.

But, again, as somebody who works in a county hospital and a metropolitan area that is under ER'd and under-doctored for a high density population like many metropolitan areas, the pandemic condition would create a situation where access to emergency rooms and physicians would be severely restricted.

So, when we talk about idealized models where every diabetic should not use this and should simply go see their doctor or try to go to the emergency room or a relatively low threshold for such recommendations in denying the potential optimal therapy or beneficial therapy is a concern to me.

I am very struck by the health models which suggest a major role for the prophylaxis component of this and that was the basis for some of my earlier questions. But having said all this, there are a couple of areas that

remain a concern to me.

Clearly, there are lots of things that, when we look at the risks, are relative and need better defining in my opinion. So, I would be interested to hear from some of the experts why the following scenario is intrinsically bad as opposed to non-optimal.

So, if a consumer has this product and decides to use it mistakenly because they hear there is a seasonal flu epidemic, and confuses epidemic and pandemic, and takes the medication totally appropriately to instructions what harm has been done? I say that as a serious question because that will occur. And, if that has some bad consequence to the individual or society I need to understand that better in making the risk to benefit assessment.

The other issue that I became actually more confused about from the discussion is the real risk of acquired resistance. Clearly, there is the possibility of there being resistance that makes the drug not effective, and for later questions I will be interested in whether there are any differences in the two drugs in that respect, but I was left without a clear idea as to whether this drug-induced resistance is really a major public health concern

and I would be interested in more expert opinion about that from other panel members.

So, those would be some of the issues that I would highlight but this is against a background, as I said, of a real public health potential benefit so that it is really refining this risk to benefit assessment to better understand how that would lay out. I have some specific comments to come later.

DR. McGOWAN: Maybe we can respond to that and maybe I can call on Dr. Hayden to give us his perspective in the sense of (a), what would happen if you took the treatment for seasonal flu. I would assume the answer is the same as has been evidenced in the pivotal studies. It would be both safe and effective to some extent unless it was a resistant strain.

DR. BRASS: So, not really a bad thing, an undesirable thing. In terms of risk, maybe not so bad.

DR. HAYDEN: Yes, I would agree in terms of that first question that use in seasonal influenza would not entail additional risk, in part because resistance issues that arise are not related, as far as we know, to what will happen with a pandemic strain unless, under some theoretical

conditions, there might be a reassortment event. But, again, these things are unpredictable. Of course, the use would waste drug so that would diminish the net overall stockpile wherever that greater stockpile exists.

With regard to risk of acquired resistance, I think that Sasha Klimov's presentation took us through that. What we do know, again, is that resistance does come up in treated individuals, generally between day four and six with oseltamivir treatment overall less than one percent of treated adults, roughly five percent in children, although if you look very carefully it is as high as 18 percent in some of the pediatric studies.

But the kinds of resistance mutations that have been observed depend very much on the circulating virus, so the type and the subtype, as well as the drug itself. So, there is variable cross-susceptibility and resistance within the neuraminidase inhibitor class. Because of the way the drugs interact with the active enzyme, as Sasha mentioned, you will certainly have some oseltamivir resistance mutations which will be maintained as clearly susceptible to zanamivir. There have been a few zanamivir resistance mutations recognized that, in fact, retain susceptibility to

oseltamivir.

DR. BRASS: I did get that. So, let me ask you two more very specific questions. First of all, do those rates of development of resistance represent a public health concern in the context of circulating virus? That is the first question.

Second, is there a difference between the two drugs that might lead to either preferential use of one and reserve of the other, like we do with some antibiotics for example in certain situations?

DR. HAYDEN: Well, the other risk is determined by the transmission fitness of the resistant variants. Most of the mutations do confer a cost to the virus with regard to replication competence or transmissibility, but it does vary. Clearly, there are some mutations that do not. We thought that 274 and N1, based on earlier work, did confer such a cost but, obviously, the current situation with H1N1 shows that there resistant variants are transmitting very efficiently from person to person with no evidence of diminution in transmission fitness. Some of this is not predictable, has not been adequately studied.

With regard to differences in the drugs, yes, as I

mentioned, there are different resistance profiles. There hasn't been a careful assessment of this in a head-to-head fashion in the context of a prospective clinical study or large analysis of the population, in part because there has been actually very little zanamivir use.

I would comment that the available data with regard to the current situation with H1N1 clearly shows that these variants are continuing to circulate in the absence of significant selective drug pressure.

I don't know that we will ever be able to know whether they originally emerged in the drug-exposed individuals. It is not likely but it is possible. I don't think we will know that but, certainly, this is a good example that was not predicted by the earlier evidence available that some of these resistant variants may be able to pose a public health threat without substantial ongoing selective drug pressure.

DR. McGOWAN: Dr. Farber and then Dr. Havens.

DR. FARBER: Most of my questions or concerns, I should say, go to those that have been already expressed and I will sort of address them later during the questions about the studies themselves.

But there are two questions and concerns I have, and maybe Dr. Hayden can actually address one of them. One is the issue of being able to self-diagnose the influenza. You know, there has been mention about diagnosis and whether patients would use the MedKit in a situation where there was a flu epidemic rather than a pandemic.

I have a bit of concern about whether patients could appropriately use a MedKit during the course of a pandemic, i.e., a situation in which a patient had, as they often present to many of usB-and please note the Aair@ quotes, a flu bug which oftentimes is gastroenteritis or other viral illnesses, and think that it is an influenza situation.

Dr. Hayden had mentioned that the diagnosis by physicians is about 50 percent against that specificity. I would hope sensitivity would be better. Even so, we are talking about a situation in which, if it were a different illness, most people would not use that as a specific test. So, I do have some concerns about that and maybe you could address that.

The second concern I haveB-and I guess some of these could be addressed during how we would do some of the

studies or how we would change some of the studies that need to be done. The second concern I have though is the situation of a pandemic is one which none of us has really ever experienced. I wasn't around for the 1918 flu. I doubt anybody in here was. The pandemics that we had later were really very mild and almost couldn't be called really pandemics.

So, the concern I have is are we really going to know how patients are going to behave in those situations? We can address some of those later, and I will address some of those later. But one of the concerns I have is are there going to be people who stockpile large numbers of kits in order to be able to take medication for four months in order to be able to prevent themselves from having influenza, which leaves no kits for some people?

DR. McGOWAN: I don't want to pick on Fred but I think a more clinical question was addressed to you, and then I think for the issue about equity of access and people stockpiling, super-stockpiling we might pick on someone from HHS. But, Fred, the clinical aspect?

DR. HAYDEN: I would just comment that in our experience with clinical trials which, again, are seasonal

influenza, in the household-based study we use the criteria for the index cases in order to initiate the intervention, which is both case treatment as well as either post-exposure prophylaxis or observation of the household contacts, a fever, and I think it was 37.8 Celsius plus cough or rhinitis. Now, that is not the CDC for influenza-like illness. When we did that roughly half of the index cases turned out to have influenza.

Now, if you look at the treatment studies where criteria, again, were broadly similar to the CDC ILI criteria but they did vary by study and some systemic symptoms were required, generally fever and a respiratory symptom and a systemic one, although I would have to go back to the specific articles, there, in the adult population, again, we saw roughly of those enrolled 70 percent that were subsequently shown to have laboratory-proven influenza, and even in the pediatric population it was 65 percent.

So, in the context of these clinical trials was that where there may be, again, more restricted enrollment the clinical diagnostic accuracy is fairly high. The positive predictive value in a study that Arnold Monto did, looking back at a large database developed in the context as

an airways trial, had a positive predictive value for fever and cough of 79 percent. The higher the fever, the higher the positive predictive value.

I would think that in a pandemic situation where the pretest probability is higher, as opposed to seasonal flu where it would be lower because of other respiratory pathogens, those numbers might actually be better.

DR. McGOWAN: Thanks, Fred. I think I am going to leave your second question to question seven because that involves availability and access issues. Tim Uyeki, we want maintain the thread as long as it is very specific to what is being talked about.

DR. UYEKI: I was just going to comment further on what Fed was saying. You know, I think with seasonal influenza there is actually a wide range of signs and symptoms of influenza depending upon age, depending upon underlying medical conditions. You know, elderly don't always get fever with influenza. I man, there is a wide spectrum.

So, there are these sort of standard signs and symptoms that we talk about with uncomplicated influenza but, clearly, there is a wide spectrum depending upon the

patient. And, I think that during a pandemic we can expect also a range of signs and symptoms depending upon age, underlying conditions, and so forth. So, it won't be just one standard sort of clinical syndrome and, clearly, during a pandemic all these other respiratory viruses that cause influenza-like illness will continue to co-circulate. I don't think they will stop.

DR. McGOWAN: Thanks, Tim. Dr. Havens?

DR. HAVENS: First, I have a comment on the initial question about the issue of the public health concern or implications about drug-induced resistance if you are taking it inappropriately.

What I understood from the CDC presentation this morning, as well as from the Roche presentation, is that a drug-induced resistance leads to a decrease in fitness, whereas, the naturally occurring resistance did not lead to a decrease in fitness. So, as I understood the presentations, then potential overuse of the drug can't be an argument from a public health perspective to not approve it.

DR. HAYDEN: Particularly when we don't have the virus. Then resistance is a non-issue.

DR. HAVENS: Right. So, I think that is an accurate representation of that. Now do I get my question? We are on question number one, I understand that. It is a challenging question because really the MedKit plan is not a plan just for stockpiling a drug but also for drug distribution. And, we are asked to comment on two issues. One is the efficacy of the drug and the other is the effectiveness of the plan.

Now, we have heard from Dr. Schwartz that the efficacy is unclear because we don't know what virus we would be treating. Therefore, we can't comment on that since we don't know if the drug will actually kill the virus at the dose that would be currently used.

So, my question then is mostly to Dr. Tegeris and it concerns the effectiveness of this approach to both stockpiling and distribution. In your slide four you showed the line that the states were trying to get to and you showed that some of the states have failed to stockpile adequate drug to support the federal plan for stockpiling, and suggested that this MedKit approach was to correct that deficiency.

You had no specific slides on the federal

stockpiling plan but you referred to a lack of distribution plans, at least in some of the states, and suggested that the MedKit plan was also a way to overcome this problem with drug distribution in the same way that it was intended to overcome a problem with stockpiling.

Now, before we suggest that companies take on what we might have considered initially a federal role to both stockpile and distribute the drug, the question is what are the alternatives to that and what studies have been done to show that this would actually have a benefit in a global way; that is, are there any studies to show that the MedKits will have uptake adequate to enhance the stockpiling of the drug to a meaningful extent, and are there any studies that show that the MedKit plan will lead to better distribution of the drug than the alternative federal plans for distribution, which we have actually not heard about?

The distribution issue becomes important in some of the issues related to equitable distribution that have already been raised. So, Dr. Tegeris, could you answer those questions about why this plan should be expected to make up for the failure of the current federal plans?

DR. SCHWARTZ: If I could answer that for John,

there are a number of questions that you asked so let me go back and try and answer a few of them. The federal strategy announced by Secretary Leavitt several years ago was that out of our stockpile target the federal government would buy a portion and that the state governments would be responsible for a portion.

Most of those states, in order to get resources to support stockpiling, have gone to their legislatures, and in some states they have been successful at hitting their target and in many other states they have not. So, there is some variability.

In terms of the distribution plans, the federal assets, the federal stockpile will be distributed to the states pro rata so that before the pandemic begins, when there is the initial pandemic outbreak, it will go from the strategic national stockpile to receiving sites in each of the states.

The states then need to make plans for how the drug would be distributed in their state, and many of those plans are not very well developed. Some of those plans utilize points of dispensing, building on the city's readiness initiative model. But those plans are still being

developed at the state and local level. Certainly, there are issues regarding accessibility.

There also are issues regarding how people would be diagnosed at the time of a pandemic. So, part of the issue is distribution and where the drugs will be dispensed, and then part of the issue is where people would be able to get medical care and get their diagnosis in a timely fashion so that they could go to that dispensing site. So, those are issues as well.

The Institute of Medicine was contracted to empanel a committee to give us recommendations on best practices for distribution and dispensing. This committee considered the issues of both treatment and prophylaxis. In the IOM's committee report to us they concluded that there was not enough information to provide recommendations on best practices. So, the process of getting this drug from these state and federal stockpiles to people in a timely fashion is still problematic.

DR. McGOWAN: Thanks very much. Let's move to Dr. Mauskapf for some insights on this.

MR. MAUSKAPF: Thank you, and I am glad you called me Dr. Mauskapf because I am not, and that has a lot to do

with my comments. I am the Director of Emergency Operations, Planning and Logistics for the Commonwealth of Virginia, specially in the area of medical surge and countermeasure distribution stockpile management.

When I look at this issue I look at it from the vantage point of mass countermeasure distribution and surge, and I do draw a parallel with our cities readiness initiative, a requirement to prophylax an entire population of a major metropolitan area within 48 hours against aerosolized airborne anthrax attack. So, I tend to have some parallels there.

We have, by the way, purchased 115 percent of our allotment in Virginia. The Governor did that almost from the git-go, right when Secretary Leavitt came to the Commonwealth. We have also purchased additional prophylaxis antivirals for our hospitals and our department of corrections and a couple of other agencies above and beyond our allotment.

This is a real tough nut to crack for us. Our plan is that we receive the stockpile and right now we have 1.5 mil courses from the stockpile in addition to our about 800,000 courses that we have on hand, and we put it out

through a distribution chain to a network of 600 pharmacies, community hold centers, dispensing physicians and others. The ticket to ride is a prescription.

Now, we are wrestling with the issue of prophylaxis, especially when you are looking at continuity of operations and continuity of government. We have spoken with the Federal Reserve Bank in Richmond and the board of governors here in the capital to discuss issues like continuity of government and prophylaxis. By the way, that is a very touchy issue as you look back at anthrax in >01 and who was getting doxy and who was getting cipro, and how that played in the public.

We think that there is a complementary relationship here. We were talking about a plan before and what studies have been done. We did a gap analysis and the gap is that, especially in a pandemic, we won't have enough physicians. We don't know if they are all going to show up, and what we do have, we don't know if they are going to be available to write script. We know that the ERs are going to be clobbered. We know that there are going to be lots of issues like that.

So, we are looking for any asymmetric response

capabilities to fill that gap. We think this one is one that at least bears study. I understand everything that was said this morning, and I agree that there are a lot of issues to be worked through. But from a planning, operational and logistics point of view, we are looking for anything that will help close that gap.

On the inequities issue, one of the things that we thought about was building more antivirals available now than they were when we started planning, so we reckoned a lot of people would be getting their antivirals through their docs and through their health plans, and maybe our 800,000 courses can be focused toward special needs populations.

If the efficacy of this home kit plan works, then perhaps that is a capital for the haves and we can focus more on the have-nots. Certainly, we are doing identification of special needs populations with our cities readiness initiative.

Special needs populations, by the way, if you break it down amounts to almost 50 percent of the population when you consider the disenfranchised, those people trying to stay under the radar and those who can’t speak English,

the mobility, the mentally and socially challenged, we are working with all those areas.

So, although I agree with all the concerns that were raised today, I think that if we can work through those concerns, and I am glad I am not a doctor because I wouldn't know how to begin addressing some of them, I think it at least bears continued study.

DR. McGOWAN: Thanks very much. Miss Swan?

MS. SWAN: This is a mechanistic question. My concern is that there could be a resistant virus circulating in a pandemic and I am wondering how long does it actually take surveillance networks to identify that and pick it up so people aren't taking the wrong medication.

DR. McGOWAN: I am going to bounce that to Dr. Klimov who also had a question. So, if you give us an answer we will give you a question.

DR. KLIMOV: Thanks. I feel that I also have some comments but let me reply to some of the remarks or questions or concerns about the resistance.

Let me start from the very last one, which is quite important. I can give you essentially just two examples. In 2005 when CDC advised against prescriptions

for amantadine and rimantadine, we had a chance to test only about 100 influenza virus samples from the United States. Normally we are receiving about 3,000 samples from the United States.

So, when you have 96 of 100 samples being resistantB-of course, I am talking about the H3 influenza at that time, it was clear that, you know, it was time to advise not to prescribe because H3 was the predominant strain at that time.

At the beginning of the 2007-2008 season we had only six samples of H1N1 viruses, two of them from Hawaii, and we already knew that those two isolates of H1N1 came from two boys, schoolmates, who played on the same football team and they came to different clinics to be sort of tested for these flu symptoms. And those were isolated in two different clinics and we did know that the viruses had been isolated before they started to be treated with anything. So, we found that they were resistant with the 274 mutation which we knew is a mutation which causes resistance.

After that we received four more samples from different other states but, you know, also from cases where we knew that it was not treated patients. So, it already

gave us pretty strong suspicions that the situation was changing. Soon after that WHO announced the results from Norway. Under the international health regulations they reported that they had a high percentage of H1N1 virus with resistance. At that time we had very few H1 viruses.

Actually, we can do this quite quickly now, especially with the increase of the surveillance which we set up here.

So, this is to some extent in answer to the question which was raised before, what happens if during the development of H5 or whatever pandemic situation a resistant virus appears? I believe that what will happen is something that happened in 2005. CDC or another organization recognized that the level of resistance to this or that drug is high and announced or, you know, advised nonprescription of this particular drug, or advised against this drug.

So, as to the possibility of developing resistance during the pandemic, of course, and I would like to stress that the situation with H1N1 viruses which we had during 2007-2008 season shows that also particular mutations which cause resistance may not be viable for the virus because usually it affects very basic function of the virus but,

nonetheless, under some specific conditions such a mutation can survive so some compensatory mutation may help the virus to survive.

By the way, previous data did not firmly indicate that the mutation for 274 leads to appearance of non-viable virus. There were some animal studies which have shown that the virus can survive.

Anyway, in this sense, from what we know now, and I have to emphasize, as Fred already mentioned, that we have much less experience with zanamivir than with oseltamivir but the data which we have right now shows that the chance of developing resistance against zanamivir is less than against oseltamivir but, once again, the scale of use of oseltamivir and zanamivir is quite different. So, the situation of H1N1 has shown that such a mutation can happen and the virus can become viable and the virus can become transmissible from one to another.

The situation with H1N1 which we has almost nothing in mutual with H5N1 as we know it now except, once again, if it happened with H1 it may happen in H5N1 but not necessarily will happen.

So, I agree with the presentation from Roche that

we have to divide resistance developed after treatment and so far there was no wide spread of those resistant mutants out of the initial cases. While in this particular case with H1N1, and this is the only particular case which we know now, the spontaneous mutation was able to survive due to some reasons, due to some compensatory mutation, or whatever.

By the way, I do not agree with the interpretation, I mean interpretation of the data from France that the compensatory mutation, probably in the neuraminidase gene according to those data, saved the virus, made it available is the only possible explanation. There are some other possible explanations. I is, you know, quite a delicate area to discuss. So, as of now, is there any risk for appearance of resistant mutants among H5N1? Yes, but we don't know the probability of that.

What I would also like to add is that from my point of view, coming back to the question now-BI am afraid I will not have an opportunity to talk over there-Bit seems to me that the most difficult part is self-diagnosis which people have to make for themselves. In this case again, you know, the development of a rapid test which could

differentiate pandemic virus from seasonal virus is one of the HHS topics and there are, you know, several developments in this area.

Also, generally speaking, I am not so much a physician actually by education; I am a lab person. But I believe that a clear label is very important. Why do I think this? Because it is a good idea to put everything you know on the website but you cannot imagine how many emails I am receiving from quite educated people who can easily go to the website but they ask me. So, I mean, not everybody will go over there. Also, there are a lot of people who don't have this access and the label should be very clear.

Also, I believe that nobody discussed this yetB-I mean, about public health awareness, etc.-Bbut nobody yet discussed the factor of a panic. Also, we haven't had experience with a pandemic yet, I mean recently to some extent, but there was a model of possible pandemic development in 1997 in Hong Kong when the first 18 cases of H5 were confirmed. Our colleagues including a team in Hong Kong watched what kind of panic there was at that time, especially, you know, in Asia and in particular, for example, it could be in China where they tried to protect

kids.

So, from this point of view, not being a physician, I would suspect that people will start, or can start to use the drugs, forgetting whether it is for prophylaxis or for treatment, especially people who can't understand a little bit the mechanism of action.

DR. McGOWAN: Sasha, could you wind up the comments?

DR. UYEKI: Yes, that is all I was going to say.

DR. McGOWAN: Thank you so much. I would like Dr. Andersen to have a chance to comment for a while.

DR. ANDERSEN: Well, this may relate down the road to some of the study design. The initial question was about risk and benefit and we heard a lot about benefit. I think it is important to think about the risks.

Right now the products have age limits. I am a parent. I have a ten-month old and there is a pandemic. That kid is going to get it, you know. I am an elder. I can't read that well so I eat all your capsules or I dump the blister packages in ice cream.

You know, it is just thinking about how to advise the authorities on what are the risks so they can balance

this against a level 5 pandemic, high mortality. That is a different risk/benefit ratio than, you know, a milder, if there is such a thing as a milder pandemic. It is looking at the packaging. It is looking at really have you just not studied it so you can't advise or are there real risks to some of these activities?

So, just looking down the road to some of the designs, but also how to advise the authorities on when is it a risk and when is it a benefit.

DR. McGOWAN: Thanks, Janet. I think I now have to try and just briefly sort of summarize question one so we can move on to the next questions and topics, no doubt, will percolate through the afternoon.

I think we were asked to address the classical sort of risk/benefit equation for this proposal. Clearly, it differs somewhat from a conventional drug advisory committee scenario. I think you have heard all of the risks and benefits. I hear I think from the committee that in particular the safety side of the equation is less of a concern, particularly as the public health benefit could be enormous in the context of a pandemic where I think it would be safe to say it would not, indeed, be business as usual

and the structures we are used to having as an interface between patients and health may not be functioning in a conventional fashion.

Nevertheless, I think it has been brought up that we wanted more granularity around sort of the general federal and state plans that roll out of responses because these impact efficacy through effectiveness. If the drugs aren't where they need to be at the right time they will never be efficacious.

I am not sure we have completely addressed this but I think there is a sense that safety is perhaps important but less of a concern. Efficacy, we have raised issues about resistance, circulating virus. Would the drugs, if they were in the right place at the right time, be effective, and distinguished to some extent between issues surrounding seasonal flu rather than pandemic flu.

I think a recurrent theme has been equity of access, and that is something which will have to be worked out as we move forward, and I think it part of the risk/benefit equation will be contingent on individuals truly understanding what they have in their home if this policy was to be rolled out, and how to use it, and there

are clearly some challenges, particularly in terms of formulations which require dose titration based on a child's age and weight, and so forth.

So, I think I would suggest that we draw a line on this area for now and then we can move on to our second question which has come up. This is actually going to be a voting question so I think what I will do is read out the question to the group today. We can have some discussion, focused discussion, and then I will tell you a little bit about the high tech voting system we have to cast our ballots.

So, question number two is will the phase 3 clinical trials that supported approvals and favorable results from the proposed consumer use studies, e.g., label comprehension, simulated use, etc., allow for safe and effective use of the MedKits by individuals who may not be under direct medical supervision at the time of antiviral drug use?

So, this is really a question about do the clinical trials support this proposal. We have Dr. Lipsitch on the list already and Paul will collect other names. Marc?

DR. LIPSITCH: Thank you. Marc Lipsitch, from Harvard School of Public Health. In terms of the safety, the concern I would like to raise for potentially considering other studies, which I think is the sub-question here, was raised a little bit this morning, and that is the question of risk compensation or, in other words, the sense that if you have the antiviral onboard you behave differently and expose yourself more.

Certainly from personal experience, that is a risk and it certainly seems in the HIV world with the availability of HAART as a serious risk, that people change their behavior because they feel that they are protected. So, it seems to me you could ask people in these sort of mockup studies that have been proposed so far, and you could also design a study conceivably to look at behavior during seasonal flue to understand whether people change their behavior and reduce their hand washing and other precautions.

In terms of effectiveness, I think this is a very unusual situation in that when we talk about whether a normal drug is effective we mean, given that a patient has some condition and is receiving the drug, are they likely to

benefit from it? That is sort of the general context in which effectiveness is evaluated for a drug.

This is very different in the sense that the relevant denominator, the relevant population is not people with pandemic influenza but people purchasing, possibly at some considerable expense, the antiviral MedKit. So, in FDA's role as sort of consumer protection organization, it seems to me that there is an important role to allow people to understand the potential effectiveness for them as a purchaser of a MedKit, rather than on the assumption that they have already been exposed to pandemic flu.

So, it seems to me that one form that that sort of effort could take would be to try to inform people appropriately of the probabilities that they would benefit from it. This gets to the issue of what people have been saying without citing any data, the potentially huge benefit of MedKits. That is why I was very anxious to say something before but it really addresses this issue of effectiveness as well so I will say it here.

At the behest of HHS, a network of modelers, of which I am one member, the MIDAS network which is an NIH-funded network of seven research groups, was asked to

comment on this, to perform modeling studies of the potential benefits of a MedKit program.

In contrast to the description of it is likely to be a very large benefit, to quote the summary that was prepared for HHS, the MIDAS consensus document stated: At the out-take and current use levels proposed, the antiviral MedKits located in homes are predicted to reduce expected pandemic influenza illness attack rates by less than two percent for any scenario examined. It continues for quite some length.

This is based on three or four independent research groups' models. So, there are lots of details which I won't go into, but let me just tell you the bottom line of why that estimate of effectiveness is so low. The first reason is that most of those who have the antiviral MedKits won't need them. The calculation there is that the expected illness attack rate with other mitigation strategies in place is expected to be between 20-30 percent. So, of every ten MedKits that are in place, only two or three of those will be in the hands of someone who becomes ill with influenza.

When you then multiply that by a positive

predictive value of somewhere less than 100 percentB-we were asked to assume 35 percent for that exercise so say 35 percent, then you go from 20 percent down to 7 percent so those numbers are switching numbers. They are assumptions but the point is that when you multiply not everyone getting infected, not everyone getting ill, and not everyone being diagnosed, most of those MedKits, because they are already in private hands, become wasted.

The flip side of this is that most of those who need it won't have it and that is simply because, at the current market rates, it is assumed that most people will not purchase it. So, between the wastage and the relatively low uptake we were asked to assume between 5-25 percent of persons would buy it. Also, the clustering among those who are well off.

Those three meant that our modeling consensus from several different groups was that the impact would be very small.

DR. McGOWAN: Thanks, Marc. Can we go to Terry Davis now, please?

DR. DAVIS: I want to focus on the patient for a few minutes, particularly low income patients and patients

that people like Ruth Parker and I have been studying with low literacy, what their knowledge is, their understanding and their ability to use health information.

We did a study that pertains to this where we asked patients how would you take this medicine, and the label said take one tablet twice daily. Of the people with low literacy, 70 percent could understand that so 30 percent could not tell us I would take a pill two times a day. When it was two pills twice a day it was less than that and, more shocking, only about 30 percent dosed out when we said show us how many pills you would take. Only about one in three dosed out four pills.

I don't have the numbers at my fingertips but we have done studies where many, many parents do not understand the difference in a teaspoon and a tablespoon. Teaspoons in your home may range from 2-9 ml. A marked syringe has proven much more effective. Patients do not want to mis-dose their children but they inadvertently make mistakes.

The other comment is cost. People at our hospital will re-dose themselves to try to make the medicine last longer because they can't afford enough or they couldn't afford enough for their whole family. I can see people

coming to my hospital who somehow had the money to pay for this, making sure it went to everybody in the family if they had one kit.

Also, just anecdotally, my mother, before she died, never threw away any medicines. So, you know, I could see these MedKits stuffed in a kitchen drawer for years.

DR. McGOWAN: Thanks very much. Ruth Day?

DR. DAY: This is a very difficult question to answer. We are to take into account two things, the results from the phase 3 clinical trials on the one hand, and then the proposed consumer use studies. It is difficult to vote yes/no or abstain partly because the consumer use studies are a good start; there are many good things in them, but they are under-specified on many grounds and so it is difficult to be able to say yes.

So, I guess the operative words in this question are Aallow for,@ you know, the safe and effective use, and the answer could be yes but they don't ensure that it will. I think that these consumer use tests have to be re-looked at.

I know this is really in question six which we will be coming to for modifications, and so on, but all the

things that we have raised today are potentially targets for testing in a consumer use study, from disposal to a variety of things, being able to recognize appropriate symptoms for influenza, and so forth.

So, it is a hard question to answer. Does it mean that if the only way for us to be able to comment on what additional studies might be needed that we should vote no? Because that is the way the question is written.

DR. McGOWAN: Thank you. Dr. Walker-Harding, I think you had a question or comment.

DR. WALKER-HARDING: Yes, you know, when I look at the word Aconsumer use@ I have a concern that we are thinking of a parent or adult as the consumer rather than possibly an adolescent. If we are really dealing with a pandemic case there will probably be a number of families where the 13-year old will be the caregiver and will need to know how to dose, you know, and take care of the rest of the family.

I didn't notice that in the studies. One of the labeling studies went down to 16. I would suggest strongly it needs to be much lower, 13 at least. As far as I know, there are no studies, the older studies that refute that a

13-year old is at least equal to an adult in decision-making around medical issues. So, I don't see why there would be a need to cut it off at 16 or 18. We really should be helping young people in thinking truly about a pandemic. There will probably be 10-year-olds, of which there are now, who are caregivers in homes. In a pandemic we know that there will be people and I am just wondering if you have been thinking about that rather than looking at adults as the only consumers.

DR. McGOWAN: Ms. Swan, you have a question?

MS. SWAN: Yes, actually it was about an additional study. I feel like we are missing two big factors here. One is physician/prescriber behavior. No one is looking at what that looks like even during seasonal flu. Doctors can get really overwhelmed then too. How likely is it for someone like my doctor to say to me, Aoh, you've got one of those kits? Just buy another one when you're done and I'll write you a script. Go ahead and take it.@ We don't know how likely that is to happen.

We also don't know something about the behavior of the viruses themselves in that there can be a real relapse rate with flu. People might feel better after taking the

medication and not be totally better and run out of things. I think we can't answer that if we don't know, but it is a consideration.

DR. McGOWAN: Thanks, Tracy. Dr. Glesby?

DR. GLESBY: Yes, I actually had a question really to the design of these compliance studies. If I understood the position presented earlier, it seemed that the compliance studies from the two companies had similar designs. One had a sample size of 300 and one had a sample size of 2,000 and I was trying to understand where these sample sizes come from. Is it just some empiric number? I don't really understand that. I am not knowledgeable enough to understand why there would be, like, almost a seven-fold different in the sample sizes.

DR. McGOWAN: I wonder if we could discuss that under question six because that is about modifications to the proposed studies, if that is okay.

DR. HAVENS: Well, should I wait until question six too, because the question really asked about studies of safe and effective use, and the question was effective compared to what. I think some of that was suggested by modeling studies. So, the question would be do we want to do a study

that would show that, or are we really focused on this very small question of does the packaging get you what you expect the packaging to do?

DR. McGOWAN: I will tell you what, we are going to vote on this and if we say no, if the majority say no then we are going to have to ask about additional studies. So, perhaps we should come back to that then. In the meanwhile, we will ask Dr. Bradley for his comments.

DR. BRADLEY: Just a quick comment having to do with consumer use and the way that both companies have rolled out their project, it is a start and when they get more information they will go to the next iteration. So, it is in process.

I think the consumer use is very critical. A few years ago when there was the pandemic scare in Hong Kong I can’t tell you how many people came to me, asking for me to prescribe medicine to them and it was very difficult to not do it. As a matter of fact, the Academy of Pediatrics had us write a public announcement for all the pediatricians to encourage them to not stockpile, noting that in Australia and in Germany drug for use for infected patients was not available because people were stockpiling it.

So, to me, when Tim and his group announce that there is a successful spread of one of these avian influenza strains in Hong Kong or Africa there is going to be stockpiling and I am very grateful to Ed Cox and the agency for recognizing that stockpiling will exist, and that this is probably the best way, working with consumers and industry and professional groups, to get it right. So, it is not in our hands to decide whether stockpiling is okay; it will happen. But it is within our hands to be able to get it right.

DR. McGOWAN: Thanks very much, Dr. Bradley. Dr. Andersen?

DR. ANDERSEN: I actually think I am going to hold off till the next one because I just have a longer list of suggestions for new studies.

DR. McGOWAN: Well, everyone has been very succinct, which is excellent. Dr. Neill?

DR. NEILL: You know, Jon Barry, the author of AThe Great Information,@ speaking at Hopkins, described the circumstance of a new level 5 pandemic as a race to the vaccine, suggesting that, in fact, any methods that were taken with regard to prophylaxis and treatment were to blunt

hospitalizations and deaths until vaccine was available. I think that is probably the case.

It is also true that, given that one example of that one level 5 pandemic, the people that were dead were the young folks. So, I am not at all convinced that it is going to be the 19-year olds or the 13-year olds that are giving medications but, rather, that excess deaths, at least in that 1918 epidemic, occurred in younger folk, and the incidence of deaths in infants and older, while higher, mimicked what you see in seasonal epidemics.

So if, in fact, what we are talking about is whether to suppose the data from labeling studies is going to inform us about what happens if that comes around again, I am absolutely voting yes, that MedKits and whatever else we can do to help slow down a pandemic would be both safe and effective, at lest given the contrary which would be to do nothing.

If, in fact, the concern is, gosh, what if it is not level 5, you know, I am willing to sleep with that. I would live with that mistake. I would not be willing to live with the mistake of doing nothing in the face of a level 5.

DR. McGOWAN: Thank you. Dr. Griffin?

DR. GRIFFIN: I would just like to reiterate what John Bradley said about the pressure to prescribe this for our families or our friends, and the feeling that, as physicians, we are withholding this treatment. I think there will be people who will get it, and who have gotten it, and I think we have to figure out a way to do it in a safe and effective way.

So, I am having a little trouble with this question also because I think the studies that were proposed are very reasonable. I don't think they are sufficient by themselves. I guess in that situation we are supposed to vote no, if we think we need more studies.

DR. McGOWAN: That really takes us to a new position where we can move towards voting. Again, the question is really saying will the phase 3 clinical trials that you have had the opportunity to review in the dossier you were sent, are favorable results from the proposed consumer studies, albeit we haven't really discussed those in any detail yet but we will subsequentlyB-would that package allow for safe and effective use? I guess that is the question we are focused on here.

So, in terms of the technology, we are going to be using the new electronic voting system for this meeting. In front of you, you will find three voting buttons on your microphone marked as Ayes,@ Ano@ and Aabstain.@ Once we begin the vote please press the button that corresponds to your vote. You will have approximately 20 seconds to vote. After everyone has completed the vote, the vote will be locked in. The vote will then be displayed on the screen and I will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did. I will add, in my role as chair, if you could very briefly describe why you voted as you did, and don't necessarily feel obliged to, that would hasten matters.

So, I guess we are ready to move towards the vote. Yes?

DR. PARKER: I am sorry, just a point of clarity. As I read this, I just want to be sure, this is to allow safe and effective use of the MedKits by individuals who may not be under supervision. This would assume like in an over-the-counter setting. So, we would be basing this

judgment based on what we know to this point has occurred in that kind of practice without a learned intermediary at the point of ingestion. The prescription goes out with a learned intermediary but the point of ingestion occurs based on label comprehension and what we would assume would be occurring without a learned intermediary based on what has happened to this point and what we know about those studies in the real world. Right?

DR. McGOWAN: That is my assumption. Someone from FDA, is that a correct interpretation? So, the product would be distributed following receipt of a prescription but, indeed, it would be taken in the absence of direct medical supervision.

DR. BIRNKRANT: I think that is the likely scenario. The point of the question is really what is the package of studies that would make people feel comfortable with appropriate results, with appropriate percentage of people responding, and we will discuss that later as well. So, what would the package of trials look like to support the MedKit concept? Does that help at all?

DR. McGOWAN: Yes, I think so.

DR. HAVENS: Again, effectiveness is in here so can

you give us direction on what level of effectiveness you want us to address in our response to this? Because we have heard that it may not be effective globally so I am having trouble understanding where you want us to focus our attention, global effectiveness or what?

DR. BIRNKRANT: Well, I think, like you implied, there are multiple meanings in here and I don't know if we can necessarily take into account every different scenario. I think we are looking at it now more conceptually.

DR. HAVENS: Thank you very much.

DR. McGOWAN: So, if I can ask everyone who is able to vote to do so.

[Electronic voting]

DR. McGOWAN: Well, it seems as though we have a vote on the screen. We have six people voting yes. We have 20 voting no and we have one abstention. I believe we now need to go around the table and people need to give us their vote. Dr. Good will be the first person and we will rotate around the table.

DR. GOOD: I voted no, and it reflects my opinion that although I like the idea of a MedKit and think it is a great idea to stockpile these MedKits, I am just concerned

about the ability of patients to comprehend and safely use these MedKits at an unknown period of time after these have been dispensed. It could be, you know, one week; it could be years after they had gotten this. And, I don't know that these comprehension studies will accurately be able to tell that, you know, at some alter period of time they will be able to safely and effectively use these products.

I am also not convinced that we have documented that these products will be effective for what they are supposed to do. A ten-day supply of these antivirals perhaps will help for a family exposure but, as has been pointed out, I am not sure what that does that for a pandemic if it is in the community.

DR. MURATA: I voted no. My interpretation of the question was the following, whether or not the previously supported registrations of these compounds, in addition to the proposed consumer studies is a sufficient product development package for subsequent potential supplement NDA and product use.

I believe, in my opinion, that there are insufficient areas that need to be explored. For example, and perhaps this can be extended to question six later,

including studies in special populations such as the elderly; as one of my colleagues said earlier, physician response; and, lastly, as others on the committee have raised, the potential to ration the prophylaxis regimens. So, for those reasons I voted no.

DR. LIPSITCH: I voted no for basically the reasons I mentioned in my discussion, concern about risk compensation or increased failure to take other precautions, which I think is study-able, and the modeling results that suggest that the effectiveness at the population level would be minimal.

DR. McGOWAN: Dr. Bradley?

DR. BRADLEY: The question is very complex and I answered part of it, and maybe should have voted differently. My understanding of the question is do we support home stockpiling and are there enough data for us to move forward, and all of the studies on efficacy aren't there; the study on consumers' ability to comprehend aren't there. But I voted yes because I believe that as we move forward all of those components will be put in place before the FDA will let this out. So, are we there now? No. The vote is can we get there? Yes.

DR. McGOWAN: Thanks very much. Mr. Mauskapf?

MR. MAUSKAPF: I agree with what Dr. Bradley said. I also believe we need a campaign or layered approach to our responses. So, this by itself is not so good, but given the others that I mentioned earlier, plus, we need to reverse the trend of everybody turning toward the government to be able to respond and cure everything.

DR. McGOWAN: Dr. Shrank?

DR. SHRANK: I voted no. One reason is there are bunch of specialty societies here that didn't seem to support this idea, and I am wondering who the doctors are that are going to prescribe this, and will it be prescribed in an equitable and consistent way?

More importantly, I am just very concerned that patients are going to have a very hard time following what will be a difficult process of diagnosing themselves and taking the medication safely. I don't think there is enough here at this point, even if these studies that are outlined work out, to demonstrate for sure that that will be done safely.

DR. GRIFFIN: I am in favor of the idea of the MedKits. I didn't feel that the studies outlined would be

sufficient. I am specifically concerned about the ability of patients to follow the algorithm and the lack of a plan to study their ability to follow that algorithm. I think we also need some information about what information physicians or healthcare providers would give to patients when they dispense these kits.

MS. SWAN: I voted no because of partial doubts on efficacy and sample size, and certain things about the phase 3 studies, but more because I don't think the studies as proposed are complete, and I will be happy to give my suggestions to question six.

DR. McGOWAN: Dr. Alexander?

DR. ALEXANDER: I voted no. Although I agree with the stockpiling concept and the MedKit, I have concerns about the details of the studies that are proposed. I am concerned, as was Dr. Griffin, about the plan for evaluating the self-diagnosis algorithm and would like to perhaps see a self-selection study on that.

I am also concerned that the individual studies just aren't long enough. I might remember what I do with the its six months from now but I am not sure in five years from now I will remember where it is let alone what I am

supposed to do with it.

DR. McGOWAN: Thank you. Dr. Andersen?

DR. ANDERSEN: I voted no pretty much for the same reasons as the last number of people. So.

DR. HAVENS: I voted no in as much as the MedKits are a part of a strategy for epidemic control and, as such, the effectiveness needs to be compared with other strategies for epidemic control. Modeling data do not seem to support further development of this strategy, and the studies proposed do not allow evaluation of this activity as a strategy for epidemic control.

DR. McGOWAN: I voted yes on this. I think the phase 3 studies show a platform of acceptable safety for the products. I think the effectiveness data showed biological plausibility of the intervention, which normally would be insufficient to get my vote but in the context of a potential pandemic I think that is reasonable. I don't think you are going to be able to do pandemic effectiveness studies. We haven't been able to do post-exposure prophylaxis for HIV infection in the non-sexual patient arena and I think this will fall into that sort of scenario.

So, I think the biological rationale is there.

The safety profile is adequate. I think there will be huge challenges in terms of the ability to educate patients to use it appropriately but those are probably surmountable so that is why I voted yes.

DR. GLESBY: Marshall Glesby. I voted no primarily because of concerns that have already been articulated about self-diagnosis and appropriate use of these products that may not be answered by the proposed studies.

DR. McGOWAN: Dr. Hendrix?

DR. HENDRIX: Craig Hendrix. I voted yes. I believe that the phase 1 studies provide adequate information on treatment and prophylactic effectiveness in a number of scenarios, although not all that would be applicable.

In addition, the compliance studies will in the future provide evidence to make judgments about the process or type 3 errors that will exist so that together there will be a reasonable extrapolation for benefits that can only be understood in the context of many other interventions that will be applied at the same time, which will be impossible to study together in a pandemic situation, except as it happens.

The only alternative, therefore, would be new efficacy studies that would combine effectiveness, compliance all over again, perhaps with some unclear answers in a decade, which I think is an unreasonable risk in relation to the anticipated benefits based on prior information.

DR. McGOWAN: Dr. Luque?

DR. LUQUE: Amneris Luque. I voted no basically because of concerns with effective use of the MedKit, in particular because of inability to follow instructions due to literacy levels, more evident in the patients that are under-insured and under-served. I am concerned about under-dosing and the other issues that were previously raised. I think we need better studies, better education and strategies to be able to say with confidence that the kits will be valuable.

DR. McGOWAN: Dr. Hewett?

DR. HEWETT: Jan Hewett. Based on the wording of the question, I voted no because I do not believe the past nor current proposed studies show safe and effective use of the MedKit for the consumer without a medical supervisor. However, I am hopeful that should this question be raised in

a future joint meeting I would undoubtedly say yes. I do believe that we will go forward in a positive way.

DR. McGOWAN: Dr. Parker?

DR. PARKER: I voted no. I feel convinced that the level of complexity of the required task to safely and effectively take this without a learned intermediary greatly exceeds that of the average American. However, I am thrilled at the efforts to advance the health literacy of us all, and think if we are able to find a way to communicate this and make it a task that people can understand that we will have a healthier America.

DR. McGOWAN: Dr. Klimov?

DR. KLIMOV: I voted no, but I am not sure that actually the question was formulated in a proper way. Like Dr. Bradley, I would say that, you know, I am in favor of the idea because a lot of people in any case will try to stockpile at home probably if there was an opportunity. But the question is about the study which was not done yet. That is why I cannot say, you know, whether it effective or not; whether it is enough or not.

DR. McGOWAN: Dr. Uyeki?

DR. UYEKI: I voted no because I think there are

additional studies that could help information these questions.

DR. McGOWAN: Dr. Davis?

DR. DAVIS: I voted no because I am concerned about patients being able to do this. I think the studies can be cleaned up, and I still have some problems with the basic concept of this, about why did the government go ahead and do this in light of what all the professional organizations have said today. I am still confused about that.

DR. McGOWAN: Ruth Day?

DR. DAY: I abstained. If you think about all the positive things we have heard so far and all of the negative things, I have both of those balances and I got stuck in the middle and so I abstained, and I do think that we need additional studies, so we will be happy to talk about all those shortly.

DR. McGOWAN: Dr. Neill?

DR. NEILL: Richard Neill. I voted yes for all the reasons that our chair did. I would summarize those reasons a little differently though. I think that it would be wise for us to mutate the processes that we use to take care of traditional risks in the face of non-traditional threats.

And, I think that the concept of study revision is helpful for level 3 and lower pandemics but don't apply, can't be studied, won't be studied except in retrospect for level 5. So, in that respect, given this is a very safe course of treatment when selected and used in the appropriate settings in the H5N1 cases, I have seen data that it is very effective. That, to me, is a slam-dunk.

DR. McGOWAN: Marilyn Eichner?

MS. EICHNER: I voted no. I am in favor of the MedKit but I am concerned about the self-diagnosis and the inappropriate use of the MedKit. I think more clear information especially needs to be for the prophylactic use versus the pandemic use and I would like to see additional studies.

DR. McGOWAN: Leslie Walker-Harding?

DR. WALKER-HARDING: I voted no. While I am in favor of the concept of the MedKits if it was universally available to people, I did have concerns that when we use it for prophylaxis versus for treatment we don't want to have a high side effect rate, and I think that there have not been enough specifically designed pediatric studies to see, on a large scale, what kind of problems we may see giving people

this medication when they do not have illness.

DR. BENOWITZ: I voted yes, and I did it on the assumption of the favorable results from proposed consumer use. There are a lot of other research things that I think should be looked at. I think it is very important to look at the consequences of inappropriate use, either overdoses or changes in health behavior, attitudes. I think there are important dose-response issues.

But if I think of the professional organizations and what their response was, it just doesn't fit with my experience. I am from San Francisco where we have more physicians per population than most places in the country but in the winter there are no ICU beds available even now without pandemic flu. You can't see a physician. It takes a week or two to see a physician. Emergency roomsB-I work at San Francisco General Hospital, six hour waits. I just don't think that there are the resources. Even though we don't have everything we need, and even with this package, it would be helpful.

Now, one concern I have is the effectiveness modeling that Dr. Lipsitch talked about. I wish I had seen that because I would like to know what that says because if

it is really not effective, then it is not worthwhile pursuing it. But not being able to see that study, I voted yes.

There is one other thing I want to bring up because I have to leave. I think there is also a need for some sort of systems research question. We are talking about two different drugs. We are talking about different resistance patterns.

I don't know if the current stockpiles of Relenza or Tamiflu, how a balance can be worked out; how we are going to deal with two different products with different resistance profiles, different use patterns. I didn't hear anything about that and I certainly would like to know more about that before a final vote but at the moment I said yes.

DR. McGOWAN: Dr. Brass?

DR. BRASS: I voted no because I couldn't find my Ayes, if@ button. I was particularly limited by the proposed consumer use studies clause because, in fact, we were not given the information I think we need to assess that question. Someone alluded to this. But you cannot assess whether a study design is right or wrong until you understand the research question in a more focused way.

And, we have not had defined for us the three, five or ten behaviors that are most critical to ensure the safe and effective use of the drug.

We don't know what the safety margin is so that if you double the dose is that clinically relevant or irrelevant? Obviously, we want them to take the right dose but how important is quantitative dose accuracy for over- and under-dosing? And, we have not defined those.

As I listened, the behaviors that were most important to me could only be addressed in a natural use study and not in the types of studies that were proposed.

Finally, I think even when we look at Dr. Lipsitch's study, which I also found very interesting, we have to differentiate the individual consumer benefit who acquired the kit versus the larger public health benefit, and think about it from the individual consumer, things like number to treat cough effectiveness, etc., because there still may be a benefit to those who actually acquired it.

DR. McGOWAN: And last but not least, Neil Farber.

DR. FARBER: I voted no and I voted no because of the fact that we are basically, I think, in a lot of ways on unchartered ground. I am fully in favor of having something

that would stem the mortality and morbidity tide of a pandemic. But, by the same token, I think we need to develop some other studies and, please, put me on the list to talk on question number six because I have a bunch of ideas but I think there are several things we need to do.

DR. McGOWAN: Thank you very much for that. Now, they divided this question and, bear in mind, we are only on the second question on the list. So what additional studies, and that is something of a Pandora's Box, I suspect, for the committee. However, we should address it. Could I ask those inclined to give us their perspectives on what additional studies and please, please, please be as brief as you possibly can, without any introductory preludes. Thank you. Dr. Birnkrant has first right.

DR. BIRNKRANT: Is it possible for us to combine that question with number six?

DR. McGOWAN: That would seem eminently sensible.

DR. BIRNKRANT: Excellent.

DR. MCGOWAN: So just to remind people on question six really, comment on additions or modifications to the proposed studies.

The committee has voted today that they wouldn't

feel this is an appropriate proposal with the current portfolio of studies. So, what else do you want, or what modifications do you want to the proposed additional studies? Yes, Dr. Farber?

DR. FARBER: So, I will give you my list. First, in terms of the modification of the current studies, I would like to make sure that there is validation of the scenarios and the questions. I haven't heard anything about that.

When you are talking about the actual use studies in terms of scenarios, as well as in the labeling, I would like to make sure that patients know the difference between flu symptoms and non-flu symptoms. I would specifically ask that they include questions in the actual use study scenarios about patients who have non-flu symptoms in a pandemic situation.

Also, in the actual use studies I think they need to ask questions about prophylaxis, both when to use prophylaxis as well as blink the prophylaxis, in order to avoid the issue of somebody stockpiling to be able to use it for four or five months.

Then, finally in terms of the actual use studies and the labeling instructions, I would like to make sure

that people understand the nature of what a pandemic is. So, one of the ways of doing that is asking the patients to repeat back to the interviewer what is the nature of a pandemic, what does it mean to you.

In terms of other studies, there are two that I would recommend. One is to do a different study which basically asks the same questions in the pandemic scenario, but do it in a model in which patients can sort of more relate to as opposed to influenza which everybody thinks of as just flu.

So, I would suggest that another study be done looking at the model of SARS, for example, which would basically be an infectious high level of mortality, high level of panic that occurs in a pandemic, and ask patients the same kinds of questions they would under an influenza.

Then, one other study I would do would be to do a combined computer video model in which patients were shown, for example, a news show, a half-hour news show, if you will, on what is happening now with the influenza pandemic, mock pandemic, that was occurring to sort of rev up the adrenaline juices in the patient, and then do an interactive thing in terms of what would you do now.

DR. McGOWAN: Thank you. Dr. Glesby?

DR. GLESBY: I think it would be informative—maybe this is a crazy idea—to have an actual use study with seasonal flu and see if people could have these medications at home and appropriately take them for treatment and/or prophylaxis in a setting of seasonal flu, which may give us some insights into perhaps the more alarming situation of pandemic flu. That is my first comment. My second is if at some point we can get back to this issue of the sample sizes of other sites.

DR. McGOWAN:: Maybe that is something we can ask them to respond to very briefly. It seemed to be a difference in sample size for the GSK and the Roche studies. If I remember correctly, which of course I don't but Marshall does—which is the smaller study?

DR. GLESBY: I believe it was the Glaxo study.

DR. MCGOWAN: So, perhaps you can justify why your studies are smaller.

DR. NG-CASHIN: Thank you. I will make a start with this and then I will have Julie Akers from Concentrics who has been helping us design these studies.

In the compliance studies we had a threshold

response of 95 percent which drove the sample sizes to 150 per cohort.

DR. AKERS: As we started to design these studies we set a priori thresholds and we set them quite high, in response to conversations that we had with CDC, HHS or FDA. Due to that, it brought the sample sizes down.

DR. McGOWAN: So it sounds as if the companies need more specific guidance about the sample size calculations methodology so they are more or less the same. I can't imagine why there would be a discrepancy. Tracy, you had a question?

MS. SWAN: It might be a laundry list of studies. I agree about using alternate media, DVD, something on TV just so people have a different way to get the information without another human there, and asking people about their belief in the efficacy of antiviral medications and vaccines just at baseline.

For the real use study, instead of one single dose for a child, sometimes people have more than one child in the household, what is it like to mix up three different doses for children of different weights? And, I am wondering if there is going to be anything done in Spanish

or other languages. Thank you.

DR. McGOWAN: I think the last question is probably easy to answer. Could the two companies tell us whether they have plans to produce Spanish version package inserts, and so forth?

DR. McGUIRE: Yes, we do have plans. Once we get finished with this part we will move into that. Absolutely.

DR. McGOWAN: And GSK?

DR. NG-CASHIN: Yes.

DR. McGOWAN: Your study modification is duly noted. Janet?

DR. ANDERSEN: I really think it is important to get more information on the risk/benefit while we are waiting for the pandemic to happen. People are going to have this in their home, if they take it inappropriately, if it is given to the wrong populations; in terms of comprehension studies to move into other populations.

The way the studies are currently described, they are taking place in clinical research centers and very often those populations are self-selected to being compliant, to being higher literacy. So, even if you get low literacy there you are getting low literacy among a high literacy

group. So, to take it truly into the community to help inform how to do the package inserts, the education to follow-up.

Somebody, I believe, had suggested some cluster randomized, in other words, multiple, multiple sites to maybe look at different techniques for initial education, potentially follow-up. Is there better retention if there is a phone call once a year, something like that?

Some of this can even be put in place once those kits are starting to roll out to refine or to really look across all users.

DR. McGOWAN: Dr. Havens?

DR. HAVENS: I would recommend studies that would look at different strategies to decrease deaths in an epidemic situation, and base those designs on reasonable models that show potential benefit. What we are talking about here is a strategic intervention that sounds like it has been modeled to have a two percent change in deaths in the epidemic.

It would seem those same modeling approaches might be used to design studies for competing strategies to compare the MedKit with having a nurse at every bar in town

with a bunch of drug, or every church, depending on your approach, or distribution by pharmacists or other standard allied health personnel, or distribution by specially trained community workers who would be put in a position.

I would argue that those studies of strategy should be done before any further development of the MedKits themselves go on since the current models of the MedKits seem to suggest that they would be of limited real benefit in decreasing mortality.

There are lots of ways to keep people out of the San Francisco General emergency room that should be explored before we get to drug in home.

DR. McGOWAN: So, just a clarification, Peter, you are suggesting we conduct randomized studies of intervention in the context of an ongoing pandemic to evaluate differential outcomes.

DR. HAVENS: No, not at all. I am suggesting that in the same way that we are looking at acceptability and anticipated activity with the MedKit, we could look at acceptability and anticipated distribution effectiveness by looking at other ways to distribute drug, both in their acceptability to families and patients, issues related to

panic, issues related to the clustering of rich people who might be more likely to have the kits and less likely to be around people who have the illness, and how to most effectively target distribution systems that might work.

This does not depend on having an epidemic. It depends on the same kind of social interventions that we are talking about now, studies of who would find it acceptable; would we think it would be more effective; and measuring the effectiveness in the same ways that we are talking about measuring it now.

DR. McGOWAN: Dr. Griffin?

DR. GRIFFIN: I just want to second Marshall's suggestion for doing the storing for endemic influenza because I think the algorithms were developed for seasonal influenza and if people can follow them and we can show that this works during seasonal influenza I think we would have a lot more confidence that we could do it during a pandemic.

DR. McGOWAN: Thank you. Dr. Uyeki?

DR. UYEKI: I was going to make the same comment. I think this should be looked at during seasonal influenza. I will just add one other thing from the pediatric perspective about pediatric dosing. I think this probably

applies more to oseltamivir for the mixing with syrup, and so forth. I don't know if you are planning to do any PKU studies to look at drug delivery, and so forth.

DR. McGOWAN: Thank you. Question from Dr. Parker?

DR. PARKER: I just wanted to mention a couple of things. I think overall this, if we do it well, can help us in explaining uncertainty, which is what I think we are trying to do. We have so many unanswered questions and we are trying to explain many things that we don't even understand.

I mean that very seriously. I mean, when I read the first line here and I try to think of how people understand that Tamiflu has not been studied in a pandemic flu but it has been studied in seasonal flu there is a suggestion that it works. You know, we don't really know and we are trying to explain uncertainty, which is a science in and of itself. So, I think we really need to take a close look at what we know about the science of really explaining things we do not know ourselves. I say that very seriously.

Very specifically, I think that the self-selection and use of the algorithm needs to be separated from label

comprehension. In Dr. Shay's overview slide there was a slide that said that it would be combined, and I think the complexity of the algorithm in and of itself would merit its own individual study, separating that from label comprehension.

I have also been a part of NDAC where label comprehension studies, although it certainly seems logical that they would always precede actual use studies and what is found in label comprehension studies would then be applied to the actual use studies. That does not always happen. This is one case where I would make a very strong recommendation that label comprehension studies be done and completed prior to the initiation of actual use studies.

In addition to that, label comprehension studies reveal findings about people's ability to understand the content of a label. Those need to be incorporated into reformatted labels that are then re-tested for comprehension prior to the initiation of actual use studies. Since I have seen times where that did not always happen, I think it is really important in something this complicated to make sure that it is done, addressing the issue of power which has been brought up as well.

The final thing would be a study that specifically relates to the ability to understand date of expiration. In my own work I have found that many people do not understand what that means, much less what it is they are supposed to do at that point.

I also have a vision of 150-200 million doses of this being available for use and then it not being used, and trying to figure out from a public health standpoint how do we get rid of this, and could that have an adverse impact on the public health on the far side, be it related to unknown things like water supplies, land use, resistance, all the things with uncertainty and things we don't know.

So, what does expiration date mean? How do we tell people to get rid of it? And, could we possibly be doing more harm than good if we don't think through this very carefully? Thank you.

DR. LEONARD-SEGAL: Dr. McGowan, could I just make a comment for a couple of minutes? This discussion is very interesting to us. I want to be certain that even though we are combining two questions here that question 6(a) does not get overlooked. Looking at target success, if people can make comments about that, it would be exceedingly helpful

for us as we sit down to help companies design these studies.

So, if anyone has particular opinions about what success rates would be. I hear people talking about specific populations that they are interested in. The concepts are excellent but it does help us as we help to design these if we know what we are going for.

DR. McGOWAN: I would hesitate in a sense, just that I am sure that members of your committee, the Nonprescription Drugs Advisory Committee, would be familiar with the concept of what percentage in these studies you would expect to answer correctly. I am not sure we would but we can have a go.

I wonder if members from the Nonprescription Drugs Advisory Committee would address 6(a), what reasonable percentage of study subjects should understand various components of labeling? I think we have already had suggestions that it can be very low. Dr. Neill?

DR. NEILL: I won't speak to label comprehension bit instead to the second portion, able to refrain from using during seasonal influenza. I do think there is data that is extant regarding prescription use of these products

for treatment of at-risk populations, for both treatment and post-exposure prophylaxis. I think there may be some data that informs either mistaken or incorrect use.

As an absolute, I think that could be considered a threshold that we would want to improve upon or at least see as a target perhaps. I wouldn't want to hold this kind of merged Rx-OTC hybrid held to a standard that is higher than the current Rx is held to.

DR. McGOWAN: Dr. Hendrix?

DR. HENDRIX: I just wanted to comment that it seems to be that, at best, it would be difficult to establish arbitrary thresholds on these. It is certainly not even as high as the thresholds that might already exist. But these studies would be of tremendous value for providing parameter estimates for larger modeling because this is going to have to be an extrapolation from seasonal to pandemic anyway.

Now, whether or not the larger model has to be part of the application, that is something for you all to sort out, but it seems impossible to assess this ahead of time with all the complex modeling that has to be done to make any sense of this.

DR. LEONARD-SEGAL: Excuse me, I would like to throw one more thing into the mix because, you know, these studies are turning in our heads. One of the aspects to the pandemic flu epidemic scenario, treatment scenario, would be the public service announcements. That, in our minds, seems to be a very important part of any kind of self-selection kind of study or actual use kind of study, and the frequency and the wording of those public health announcements, none of which we have yet seen.

I wonder when you talk about seasonal flu scenarios if you have in mind some kind of announcement that would be similar to a pandemic flu announcement that would be incorporated into the scenarios that you are talking about. I am trying to understand better the focus of this study that is being discussed.

DR. McGOWAN: Maybe we could go to Dr. Day. Perhaps she might like to comment on that.

DR. DAY: I am commenting generally on this question. One thing that has not been brought up for a compliance studyB-all we have heard about compliance studies is they bring back and make sure that all the drug is still there. I would like to make sure the instructions are still

there too. As I understand it, the package insert, patient brochure, whatever it is, is going to be in the carton. Are people going to open the carton and read it first and then set it down? So, do they still have the instructions as well as the drug?

I do agree with Dr. Parker that too much can get thrown into a label comprehension study. It might not be bad to do a little bit of a lot of things the first time but I am convinced that a separate study needs to be done on self-selection and other selections, dosing for other people in the household, and so on.

I would echo an earlier comment that I think we do need a physician study about comprehension and prescribing. In order to set a level of what level of comprehension we need, we need to know more about the consequences. So, to go back to something that Dr. Brass originally raised, what are the consequences of an overdose or a certain amount of overdose? If it is really huge, then we would want the comprehension rate to be higher. If it isn't so bad maybe we would be a little more relaxed. So, that is one of the problems in being able to answer the question about the percentage of comprehension.

DR. LEONARD-SEGAL: The problem is that we have to answer that question because as we design these studies we are going in this direction now. We use our best medical judgment on this, however, people have different opinions and we are interested in hearing different opinions.

DR. DAY: In your last Rx to OTC switches that got approved what was the comprehension rate for self-selection? Was it about 85 percent, or do you have that information? Or, are you perturbed that I ask?

DR. LEONARD-SEGAL: I can't remember all the numbers. I do know that with the orlistat we had an expectation, for the subgroup of people that were taking cyclosporine because they had received an organ transplant, that 100 percent of those people would get that correctly and they did. However, we had different thresholds for other groups. And, I don't think I am hearing from the group that we are talking about that kind of a scenario in this discussion today.

DR. McGOWAN: Dr. Walker-Harding?

DR. WALKER-HARDING: I had two things. One was a question for GSK. I was wondering if you have any plans or you are already studying, looking at single dose nebulized

medicine for those under five, or spacers, or what kind of methods are you looking at so that the vehicle can accommodate kids under five?

My other comment in terms of a research project that hasn't been mentioned is, looking forward to the future of trying to grow a nation of people who know how to deal with and understand pandemic versus epidemic, home stockpiling and even how to possibly dose this, I think it would be nice to evaluate the education system and see if some of this can't be incorporated in health literacy or emergency preparedness. We do that for a lot of other things like earthquakes. I don't see why this wouldn't be something that couldn't be incorporated in a curriculum if the education community felt that it could be.

DR. McGOWAN: Maybe you could ask GSK very briefly to respond to that, so dosing in younger children.

DR. NG-CASHIN: Thank you. Relenza is formulated in a lactose dry powder. The Diskhaler device requires, as we talked about, assembly and then puncturing of the blister and then an inhalation. Because it is a dry powder it is not a metered dose inhaler. It doesn't require timing between activation of the device and inhalation so a spacer

isn't appropriate and it is kind of why the device was developed in our prophylaxis and treatment studies.

The opinion of our data package was that children under five couldn't reliably inhale from the device. At this point we don't have plans to study this particular preparation in children under five, and we don't have any other formulation options available for that age group at this point.

DR. McGOWAN: I am going to take one more question or comment on this specific of question from Dr. Farber, and then we will have to move on.

DR. FARBER: Just addressing question 6(a), I am new to the committee so I really don't know the previous studies. I can tell you that basically what is usually taken as medication adherence for prescription drugs in terms of a physician prescribing it and, hopefully, instructing the patient and the patient taking it appropriately is usually listed as 80 percent. So, I would think it would be around that number.

DR. McGOWAN: Just to draw this question to a conclusion then, the committee has voted as you saw. The additional studies seem to have focused primarily, I think,

on expansion, modification of the already proposed studies in terms of comprehension and use, and so forth. I think we would liken that to a little bit more real world in terms of the design characteristics.

There has been a requirement or suggestion for more operational studies in terms of rollout distribution; perhaps prescription behavior from physicians, and so forth.

Other than perhaps looking at subgroups of at-risk groups, pregnant women, very young children, and so forth, perhaps the consequences of under- of overdosing, not a huge amount on safety and no specific recommendations about effectiveness.

But I think we can now move on to question three, which is to comment on the use of a MedKit for treatment versus prophylaxis of influenza during a pandemic. Specifically, taking into account the characteristics of the drugs included in the proposed MedKits, are both treatment and prophylaxis indications appropriate for the MedKits as designed for both of the proposed products? If both indications are appropriate, is it acceptable for the same MedKit to be used for both indications? Would anyone like to begin with that? Dr. Farber?

DR. FARBER: I would like to address the second part primarily. I think that basically the MedKits are appropriate for both prophylaxis and treatment. I have concerns about them being combined in one kit, and that is, I can see where patients might either get confused or might think that, well, if prophylaxis is a good thing then doubling that prophylaxis is even better for prophylaxis.

That is a hypothesis. It is a testable hypothesis, and unless I see data to the contrary, i.e., some studies to prove it, I would have concerns about mixing the two because of the possibility of people either overdosing for prophylaxis or under-dosing for treatment. So, I would suggest that they be separated unless there is data to support the fact that that does not occur.

DR. McGOWAN: Mr. Mauskapf?

MR. MAUSKAPF: I will approach this also from strictly an operational, logistics perspective. If you consider the duration within a community of about eight weeks, then you are talking about potential for 1:8 ratio in looking at the amount of drug that will actually be used. So, from that perspective, I don’t support it for prophylaxis.

The national stockpile has set aside a certain amount for prophylaxis and that would certainly be made available to the states for that purpose but I don't support it for here.

DR. McGOWAN: I think Dr. Bradley's hand went up first, and then Dr. Lipsitch.

DR. BRADLEY: Just very quickly, I want to differentiate between intra-family prophylaxis so that if someone in the family gets sick, then I think it is appropriate to use prophylaxis. And, somehow that needs to be made really clear in the MedKit and I am not sure how that would be done, but a differentiation that is clear.

In terms of community prophylaxis, the issues of prolonged therapy, having enough drug, knowing when to start and when to stop, if you think the others are too complex, this one is really too complex. So, I would leave that up to our government people to provide community prophylaxis.

DR. McGOWAN: Marc?

DR. LIPSITCH: Yes, while I have some general reservations, I can't kind of separate those two uses from one another as long as it is clear that it is post-exposure prophylaxis or family prophylaxis rather than long-term

prophylaxis, in part because both of them, in the Tamiflu case which is exactly the same number of the same size pills, it seems to me if we are worried about any kind of misuse the most likely so-called misuse would be using it for treatment instead of prophylaxis, or vice versa, and it would be important to have instructions for both so that at least people will do it correctly.

DR. McGOWAN: Dr. Griffin?

DR. GRIFFIN: I would agree with having them both because I think if a family member is sick you want to also have the prophylaxis for the other family members. Obviously we want a study where people can understand that, but I think it is convenient that it is the same number of pills for both.

DR. McGOWAN: For clarification, you would be happy if the boxes looked identical. The trick would be that they would have to educate the families appropriately that it is the same box, the same tablets. That is what you are supporting? Dr. Havens, did you have a comment?

DR. HAVENS: Thank you. It is a question for Dr. Hayden who, on his slide number 28, showed that the benefit of prophylaxis adds dramatically to the benefitB-I think he

has gone? Lipsitch can handle it; he is the modeler or, actually, is Dr. Tegeris still here or one of the HHS people? Because the question is there are two types of prophylaxis that we are talking about, either seasonal which might be eight weeks, versus family which would be five days or ten days.

The question is are these benefits of prophylaxis as modeled, either by HHS or Dr. Hayden, different? So, what prophylaxis is best? The State of Virginia makes it seem like they have made a decision to not prophylax, except rarely, seasonally.

MR. MAUSKAPF: The decision to prophylax will be more accepted early in the disease. Once it gets going, then not so much.

DR. HAVENS: And that might be seasonal prophylaxis.

MR. MAUSKAPF: No, no, none of the stockpile is for seasonal; it is all for pandemic.

DR. HAVENS: So, it is all post-exposure prophylaxis.

DR. McGOWAN: I think you are confusing this, Peter. You are using seasonal instead of saying seasonal

influenza. You don't have pandemic in that. Seasonal outbreaks of family outbreaks?

DR. HAVENS: No, when it is in your community would you start prophylaxis to cover the time that it is in your community? So, that would be the focused seasonal prophylaxis.

DR. McGOWAN: Can I ask Dr. Schwartz to maybe address that because he discussed it a little bit earlier?

DR. SCHWARTZ: HHS guidance has been put out for public comment. We have gotten comments. It has been revised and, hopefully, it will be finalized very soon. It recommends seasonal prophylaxis for the duration of a pandemic outbreak for certain occupational groups, for healthcare workers, for emergency service responders because those are groups that are at high risk. They have high occupational burden and that is the type of prophylaxis that is most likely to get them to work so that they can meet those burdens.

In terms of households and individuals, the recommendation is for post-exposure prophylaxis and, as you heard from the studies that Dr. Hayden presented earlier, these drugs are very effective for household post-exposure

prophylaxis for seasonal influenza, in the 70-90 percent range.

So, there is no reason why an individual or a family could not take longer-term prophylaxis but in terms of the modeling, in terms of the expectation, that wasn't what we were using.

The CDC community mitigation guidance, which also has become part of our pandemic response policy, suggests household post-exposure prophylaxis if drugs are available and if a feasible strategy can be developed for implementation.

DR. McGOWAN: Thanks very much. I think we need to move on to question four. My sense on question three is that there is broad acceptance of the fact that the indications were appropriate for both treatment and prophylaxis. There was some concern raised that we need to ensure that the individuals receiving the intervention will be aware of the difference.

I think question four is much more tailored. In a sense, you are asking here about Tamiflu, and in particular for dosing children through the use of the contents of the 75 mg adult capsules although Tamiflu is also available

commercially as 30 mg capsules and 45 mg capsules, as well as an oral suspension.

So, what is the most appropriate formulation to be used for pediatric dosing in this setting? So, maybe I can just ask Roche to just very briefly just remind us, you addressed this earlier today, about your rationale for what you chose to do and I think comments about the stability of the suspension too. So, your current plan.

DR. McGUIRE: Sure. Slide up, please. The reason for the 75 mg dose, as you saw in the presentation, children are dosed by weight. We also have included in the MedKit booklet age as well. But let's assume we are dosing them by weight, as children get older they get heavier. They fall into another dosage. So, when they may purchase a MedKit, if you had a 30 mg MedKit out there, as they got older that would be obsolete for them and you would be under-dosing them if you used it.

So, our thinking was to avoid that confusion of what is the dose I give now that my child has gotten older, we stick with the 75 mg dose which will allow us then to tailor that dose through the suspension, through chocolate syrup or whatever way. We have a couple of other vehicles

in which it could be provided.

We do have stability data, palatability data and preserver efficacy data surrounding that. So, the idea was to try and make it as simple as possible, instead of having multiple MedKits in a family setting, by having one.

DR. McGOWAN: That provides your rationale. Clearly, there are formulation options, other dose capsules. Perhaps Dr. Bradley would be a good person to respond to that.

DR. BRADLEY: Thank you. As a pediatrician, the stability I think is very important, and I have some concerns that parents may not be able to correctly put together the correct dose for each child as they get older, and the concept that tablespoons and teaspoons are difficult for many parents to differentiate between worries me a lot.

I think that the capsules, all the way down to 30 mg, should be used and I think, in addition, that there should be something for children where there should be a little form that you can add to each year. You weigh your children and you have an assortment of capsules, 30 mg, 45 mg, 60 mg, and before the pandemic hits you weigh your child each year. You get a weight and then you write down how

many capsules that child should get if the pandemic should hit that year.

So, I think that the capsules actually would be a preferred way to go, but I am certainly willing to say that the comprehension studies may prove me wrong and maybe the solution is the best way.

DR. McGUIRE: Just one more point-BI am sorry, Dr. McGowan. The 30 mg and 45 mg would still need to be broken. They would still need to be put into a mixture. A child less than 33 lbs cannot swallow a capsule. So, just so you know that you would still have a mixing process involved with regards to that.

DR. McGOWAN: Thanks very much. I am assuming the U.S. stockpile is just the 75 mg dose. I am seeing nodding of heads. Dr. Schwartz?

DR. SCHWARTZ: Some of the 30 mg and 45 mg capsules are being purchased as well for the stockpile.

DR. McGOWAN: So, potentially there is flexibility or at least grounds for further discussion on this topic.

DR. SCHWARTZ: Yes.

DR. McGOWAN: Thank you. Dr. Alexander?

DR. ALEXANDER: I find it a little bit surprising

that the pediatricians haven't commented on the age-based dosing compared to weight-based dosing, the dosing that is recommended. I think the weight of children in this country is significantly variable so it concerns me that we would be not basing dosing on weight.

DR. McGOWAN: I thought we were.

DR. HAVENS: You are right, there are two options in the package insert. One is by weight, if you have it, and the other seemed like it was by age if you didn't have the weight.

DR. McGUIRE: In the current package insert that is on the market it is by weight but the thought was that in a pandemic children, if you don't have a scale in the home and you are wondering what to give your child, age-based dosing would be another way to approach this. That is why you see that in the MedKit booklet.

Now, we have done work correlating age-based and weight-based dosing. If you like, we can go through that. I will leave that up to you, Dr. McGowan.

DR. McGOWAN: I think in the interest of time and other questions to be resolved we might just pass on that. Any other questions from the committee about this topic?

DR. PARKER: It seems like this is a wonderful opportunity to really look at a standard dosing device and the ability to really sort of advance what happens in pediatric dosing with that. The data are very clear about lack of understanding of a teaspoon even among physicians who prescribe that people take a teaspoon of a medicine. There are many physicians who can't accurately pick out a teaspoon from a selection of spoons in a household, so I think including that--and I think we could do a great study here in the room of that.

So, I would say that this is great place to use a standardized dosing device and to sort of advance what we all do with that and to be very clear about that.

I have some trouble with this little bowl and these little pictures, and how many spoonfuls you put in here, and how you mix this stuff up. So, I would say this is an ideal opportunity to also look at people's ability to understand this and actually perform it accurately.

I assume, for product liability, this is more the errors that occur in dosing and, on the other side of this, this will sort of fall out more with a prescribed medication or an over-the-counter medication. So, I think there are a

lot of issues that our associations brought up that really merit further consideration.

The other thing is the advertising for the use of this and what it actually contains in terms of encouraging the sale of it versus the information for accurate, safe and effective use without the supervision of a learned intermediary, really, this is just going to be great if we can get there.

DR. McGOWAN: Thank you. Dr. Walker-Harding?

DR. WALKER-HARDING: Just a quick question, with the dosing and the possibility that in a pandemic we may need higher doses, what is the window of safety for kids, and are there some weights that could actually be at 75 so you actually have less people that need to be dosed with measurement?

DR. McGOWAN: Would each of the companies like to address that topic very briefly?

DR. McGUIRE: Sure. We do have information with regards to that. I would like to invite my colleague, Dr. Regina Dutkowski.

DR. DUTKOWSKI: In the clinical trials we studied treatment for five days and also looked at post-exposure

prophylaxis in children over a ten-day period and we recently have completed a six-week prophylaxis study in children.

In some of the studies there were some dosing errors that were made by the parents in dosing their children. However, the safety margin is very wide. And, when we look at the safety profile, in each one of those scenarios the most frequently reported events were gastrointestinal with small increases seen in the treatment scenario as compared to the prophylaxis scenario. So, there were no obvious signs of overdose from dosing in a small proportion of the patients.

DR. WALKER-HARDING: Then is it possible for people to all have 75?

DR. DUTKOWSKI: I think I would need to defer this question to my clinical pharmacology colleague.

ROCHE REPRESENTATIVE: Slide up, please. In the last column here we have the actual approved unit doses, 30 mg, 45 mg and 60 mg. In the first column you can actually see the weights and, as you can see, the upper weight here is 80 lbs for 60 mg. So, any child who is over 88 lbs or over nine years old will actually get the 75 mg dose.

DR. McGOWAN: Thank you. Can we perhaps turn to GSK for comments?

DR. NG-CASHIN: As you know, zanamivir is delivered by inhalation and is, therefore, a topical delivery. Doses above the recommended dose for both adults and children haven't been studied specifically in children, but I can say that in adults intravenous doses as high as 1,200 mg have been given with no significant adverse effects, implying that our safety cover in children would also be well covered by over-dosage.

DR. McGOWAN: Yes, Dr. Good?

DR. GOOD: I am just curious, have either of you looked at patients who might ingest both drugs together? It strikes me that in an epidemic/pandemic situation some patients, since the routes of administration are different, might be confused. Zanamivir is targeting the respiratory tract and oseltamivir is, you know, taken orally. So, they might have different mechanisms of action. Being confused, they might be confused and take both. So, is there any safety data on taking both together?

DR. NG-CASHIN: From GSK there are no direct safety data examining subjects who have had the co-administration

of zanamivir and oseltamivir. As we have heard, they do share the same mechanism of action. From an efficacy standpoint whether that would be additive, synergistic or antagonistic I don't think we know.

In terms of the bioavailability of the inhaled dose of zanamivir to the systemic circulation, it is I think around 17 percent. Both drugs are cleared renally and, based on what we understand about the metabolism, we wouldn't expect a significant drug interaction based on preclinical data.

DR. McGOWAN: Would Roche like to comment?

ROCHE REPRESENTATIVE: Slide up, please. We have looked into all postmarketing data for combinations of Tamiflu with other antivirals and basically can confirm what has been said. The AEs we have seen were either related to the underlying disease were labeled or confounded by the indication. So, we didn't see any kind of drug-drug interaction or change in the safety profile by the combination of zanamivir and Tamiflu, although there are very few cases.

What we are currently planning is an interaction study or combination study of zanamivir and Tamiflu and we

will report the results when they become available.

DR. McGOWAN: Thank you very much. Dr. Andersen?

DR. ANDERSEN: Something to point out with the dilution of Tamiflu is that it is a dilution. As long as the same spoon is used for the preparation and the dosing, it doesn't matter what size the spoon is. So, you could use a tablespoon as long as you use the same spoon over the time that you are storing it and re-dosing the child. If you make the dilution with a tablespoon and then a couple of days later you use a teaspoon, then you are under-dosing and vice versa.

DR. McGOWAN: I think in terms of question four, I think we have reached a point where for pediatrics probably choice is important. There is perhaps choice in the U.S. stockpile. There is clearly work to be done in terms of determining whether or not, indeed, parents could reproducibly and appropriately formulate the drug in the various tasty options that are being provided. And, I think that is about as far as we have gone.

So, now we are going to move on. We have touched on this already but we are going to move on to question five, which was to comment on specific elements of labeling,

packaging, or instructions that are critical for safe and effective use of a MedKit. This certainly seems to be a question which I will begin by directing--and the hands are going up already--to my colleagues on the right, so Terry Davis first of all.

DR. DAVIS: When I was looking at this I think the label could be improved with using bullets and better, headers, and more to the point headers.

But I was curious, have you all done focus groups? Do people understand the difference in Atreat@ and Aprevent@ and Aseasonal@ and Apandemic?@ You know, we are assuming that those things are understood and then we are going to tell you how to dose these things. I just wondered what have you found out in the studies that you have done?

DR. McGOWAN: We will have an answer to that question from both companies again. Have you done focus groups on your marketing packaging rollout products?

DR. McGUIRE: Slide up, please. We did do some research. We did find in some research of about 200 people that they did well with regards to the media pandemic. There are directions for use and warnings contained within the MedKit booklet.

The area that was not as well comprehended was around the treatment algorithm. We are currently working with folks at HHS and their colleagues and GlaxoSmithKline to improve that.

DR. DAVIS: What did they say pandemic meant?

DR. McGUIRE: Since I was not physically there I will ask Dave Bradford to come up and comment.

DR. BRADFORD: Well, I wasn't physically there either but I looked at all the answers. They understood pandemic really quite well and understood that it meant widespread, epidemic-like. Approximately 80 percent of people, when asked the open-ended question what does pandemic mean, gave a response that was clearly in that general domain.

I might just also comment with regard to the treatment algorithm, one of the reasons why the results turned out somewhat more poorly there was because people who were unsure about what to do adopted the most conservative course and indicated that they should consult an emergency room or a physician even under circumstances where the algorithm would have suggested some other course of action. So, there were errors but they were errors in a good

direction.

DR. McGOWAN: Thank you. GSK?

DR. NG-CASHIN: At GSK we have not yet had the opportunity to conduct any studies, but certainly pandemic versus seasonal and the other things you mentioned will be part of what we test in our labeling comprehension.

DR. McGOWAN: Thank you. Dr. Glesby?

DR. GLESBY: Most of my patients come from under-served backgrounds and do not have a thermometer at home so my simple suggestion is to include a thermometer in your packaging.

DR. McGOWAN: Dr. Farber?

DR. FARBER: A couple of things. One is I am not sure how much people understood how to diagnose themselves with influenza in terms of the fact that simply because one has fever and cough doesn't necessarily mean they have influenza, although it is a high likelihood. So, I would want to make sure not only in terms of the fact that they were having the right symptoms for influenza, but that they were not having other symptoms that would not go along with influenza. I think that should be clear in labeling.

Then the second thing I would include in labeling,

to be sure, is that there is information about what prophylaxis means versus treatment, and for how long, and the fact that one should prophylaxB-assuming that we are doing it just for post-contact, just for close contact, and that prophylaxis is not indicated and shouldn't be done.

DR. BRADLEY: If I ca take Neil's statement and go just one step further, the package labels currently address taking the right dose in the instructions to the patients. What we are doing now is extending that to a completely different realm. We are asking patients to diagnose an infection.

So, package labels have never included that, to my knowledge. So, whether the algorithm that was presented by HHS should be in the package label or not in the package label or be sort of in the kit as information is probably an important item to discuss.

In terms of the packaging itself, in everything that I have read these doses are specifically for the pandemicB-specifically for the pandemic. No one is to use it for anything else. And, it seems to me that as I look at the box, it is the Tamiflu, you know, sunshine burst thing and if they could change that and have Tamiflu in different

colors, maybe Tamiflu PB, for Tamiflu pandemic and Relenza PBB-there has to be something on that label that makes people know this is not your standard, regular issue drug. It will just get some people to think, wow, maybe this is different; maybe I shouldn't do it.

DR. McGOWAN: Thank you. Dr. Lipsitch?

DR. LIPSITCH: One thing that makes this drug different from almost any other is that the duration of time between sale and expiration directly determines its value. Right? So, if I buy Tamiflu to use tomorrow I don't care if it is good for six weeks or six months or five years.

So, not only does the expiration date need to be prominent in a way that it maybe it doesn't as much for other things, but it might be appropriate to restrict sales in a different way so that the consumer gets the value of some number of years of use out of this, rather than however long it sat on the shelf in the pharmacy.

DR. McGOWAN: Thank you. Tracy? Pass? Dr. Murata?

DR. MURATA: I had a very simple question for Roche. Is the proposed mock packaging real size as shown in the booklet here?

DR. McGUIRE: it would fit inside the blister pack

so it is pretty close to that size. Each one of the MedKits would be in the packaging, sealed, and that way it wouldn't be lost.

DR. McGOWAN: Dr. Shrank?

DR. SHRANK: Two things, first, if Tamiflu is a class C pregnancy drug and if we think it really is an important riskB-right now it is on page 12 and not really very prominent in this little booklet. It seems as though that could receive more prominence.

The other thing, in this discussion we have kicked around both the prescription form and an over-the-counter form, not very explicitly with regard to the over-the-counter form.

But were this to be an over-the-counter drug I think that we would have to do a whole different sort of set of actual use and, most importantly, self-selection studies. For self-selection studies I think the most critical kinds of studies would be to make sure that people with upper respiratory infections aren't walking down the aisle in their local pharmacy aren't picking up this package for their symptoms.

So, as this process progresses and we think about,

you know, ultimately where this product is going to be stored and what the process is going to be of getting that product, I would encourage you to pick the right test for the right place.

DR. McGOWAN: Dr. Brass?

DR. BRASS: I think Dr. Bradford may have sort of highlighted some of the concerns I have with the entire consumer research design effort because I am quite convinced they don't understand what pandemic is.

Every season in every community the news says we are having a flu epidemic. If the epidemic and pandemic are synonyms to the consumer, then every season we are going to have the use.

So, again, I think this emphasizes that the design has to be to challenge the model, not to confirm preconceptions, and to center around the really critical issues because I continue not to hear explicitly stated what the consequences of non-heeding are.

For example, if I go 12 months past the expiration date how much loss of potency do I have? Are any of the degradation products toxic? What are the concerns I have if I store it for 12 months too long, 24 months too long that

help me answer Dr. Leonard-Segal's earlier question because it is the consequences of non-heeding that determine the thresholds and accuracy in well designed consumer trials that are designed to address those specific points.

DR. McGOWAN: Thanks very much. Dr. Farber gets the last question in this segment.

DR. FARBER: Just looking at the algorithm and the labeling in general, it is fairly complex and I am wondering, for both companies, if you have done a reading level?

DR. McGOWAN:: Quick question, reading level?

DR. FARBER: On the algorithm as well as the labeling instructions.

DR. McGOWAN: So, the algorithm belongs to Dr. Schwartz. I guess the companies will talk about the labeling.

DR. McGUIRE: I mentioned to you before, that study we did before did include both the algorithmB-it included all the information within the MedKit booklet, which included the algorithm and specific information with regards to it.

DR. FARBER: Specifically the reading level?

DR. McGOWAN: The question was did you evaluate the reading level at which these materials would be comprehensible?

DR. NG-CASHIN: We have not done that yet at GSK.

DR. McGOWAN: At Roche?

DR. McGUIRE: We plan on testing that.

DR. DAVIS: I did a lexol [ph] on both of those and they were both 10th grade I think. But, I mean, it could be formatted better, both of then could.

DR. McGOWAN: So, I think we have had some input about the contents, about the modifications that might enhance the suitability, appropriateness of use, etc., and that is probably work in progress, I imagine.

We do have one remaining question, which Dr. Shrank touched on. I just want to ask Dr. Birnkrant shall we try to move into that as we have a little bit of time?

DR. BIRNKRANT: I think that is a good idea.

DR. McGOWAN: So, let’s go to question seven, which is really talking about the availability. I think for most of today we have really been focused on the concept of why individuals at some point would receive a prescription from their healthcare provider. They would then obtain the

stockpile product and it would be at home for a period of up to five years.

In this scenario we are exploring basically, well, what about if we would move to more of an OTC availability system? Specifically the question is asking if availability without a prescription is considered an option, please describe any additional studies that would be needed to support a switch from prescription to nonprescription availability.

So, again, would anyone from the nonprescription groupB-Dr. Good is going to comment first of all.

DR. GOOD: What we are looking at is potentially having tens of millions of prescriptions of these antivirals sitting around houses; maybe being stored appropriately; maybe not being stored appropriately if the patient doesn't have air conditioning; maybe sitting around for five years; maybe being replaced. Patients may be taking them for the common cold; maybe not; maybe having adverse drug reactions; maybe not.

The question that I have that I haven't heard, in terms of thinking about it and trying to answer this question and to answer these questions in general, is what

is felt to be the likelihood or the possibility that we might have one of these pandemics within the next five years.

You know, we are going to expose perhaps tens of millions of people to these drugs appropriately or inappropriately. So, are there any estimates of what the possibility is? Has anyone generated a likelihood that we might have a pandemic flu?

I was just going to say when you review the literature everyone says we will, but when? The definition I guess is what is the statistical likelihood of various finite time stance?

DR. SCHWARTZ: As you would predict, but we can't tell how likely it will be within five years.

DR. McGOWAN: Thank you. Let's get back to question seven, after that slight detour. Switching from prescription to OTC, Dr. Day?

DR. DAY: If there is a switch to OTC there are implications for direct-to-consumer advertising. Direct-to-consumer advertising of OTC drugs does not require the same level of reporting of, say, side effects and warnings, and so forth. So, we have to be very careful about going that

route.

I would like to include in this question, if we could, a discussion of a behind-the-counter options, if that would be all right.

DR. LEONARD-SEGAL: I just might make a comment that currently, you know, under current law there are only two mechanisms of drug availability. One is prescription and one is OTC. This is a strange product so I don't know where that goes, but I can tell you that the legality of this right now in terms of drug marketing is Rx and OTC.

DR. DAY: There are cases kind of in the middle, such as Sudafed is now kind of behind-the-counter because of potential problems with it.

DR. LEONARD-SEGAL: That is DEA, not FDA.

DR. DAY: Thank you.

DR. McGOWAN: I suppose the sub-text in that question is maybe for Dr. Birnkrant, would the FDA entertain a proposal from the sponsor to consider a third pathway, or how that process could be evolved? We have two polarities. We have prescription only or we have OTC. There isn't a middle ground, but is there a process to even begin to think about that given the unusual context of pandemic flu and the

need for various options?

DR. LEONARD-SEGAL: I think maybe I can try to answer that for you. None of us has had this discussion I think internally. We have a lot of sponsors that have expressed interest in alternative marketing venues of one variety or another that have come to the OTC group to talk about their ideas.

A year ago there was a Part 15 hearing that the agency held that looked at the behind-the-counter marketing possibilities. It was really a hearing for the agency to sit and listen to different opinions. There were conversations that swirled. Right now we are where we are and I think that there has been nothing specifically brought to us about alternative mechanisms for this particular product. Even though it is a unique thing and it is coming from HHS, those discussions haven't been happening. That is just a background for your conversation.

DR. McGOWAN: We have Dr. Havens next to me.

DR. HAVENS: What is interesting because from my perspective allowing OTC evaluation and rollout of these drugs answers many of the problems that I have with the current MedKit concept. So, allowing the consumer to buy

the dose that is appropriate for their child and the dosage formulation appropriate for their child this year, potentially using it in a way that we might not know is appropriate or not, would allow us to measure the appropriateness relationship to resistance and would put full control with the consumer.

One thing that is a problem with the MedKit approach is that it mixes the federal approach or the socialistic approach with the completely libertarian approach. And, perhaps the completely libertarian approach of the OTC gets around many of the problems related to that kind of a mixed approach.

And, I find myself really supporting OTC development as it would allow us to gain a lot of information that would speak to the potential utility of the strategy of the consumers buying the drug themselves. You would get to all of a sudden know how many people would buy it; if use would be appropriate; and measure its use and impact on resistance.

DR. McGOWAN: Dr. Neill?

DR. NEILL: I would favor its approval in the OTC setting, in part because in a pandemic, worse-case scenario,

speed is of the essence and, you know, trying to distribute to Virginia by my rough calculations means 2,600 completed prescriptions in the hands of patients per minute, every minute for the 48-hours that you said is a deadline, if you want to get the whole state. You can parse that down however you would like, it is still an incredibly complicated procedure.

MR. MAUSKAPF: We are doing it for treatment. So, it is spread out over the duration and it is not going to be 7.4 mil; it is going to be the affected population.

DR. NEILL: Understood and, yet, I think I heard that under this in your current strategy it is triggered by a prescription. The wait times to get a phone call in my office approach 48 hours. So, I think we need to consider the OTC environment.

Then, in terms of additional studies, I think, as has already been mentioned, I want to emphasize the need for actual use studies given the paradox that I hope there never needs to be a actual use in a setting in which it is likely to be most in demand.

DR. McGOWAN: Dr. Neill?

DR. NEILL: Could I just make a comment with

regards to safety reporting? The comment was made that the safety reporting was different. This would be an IND/NDA product. Safety reporting, either whether it is over-the-counter or prescription, is exactly the same as far as the companies are concerned in submitting things to the FDA. I believe Dr. Leonard-Segal maybe can comment, advertising has some differences.

DR. LEONARD-SEGAL: Yes, safety reporting for OTC NDA products is the same as for Rx NDA products. The advertising, however, for OTC products is governed by the FTC and that is a difference with prescription products where for prescription products the FDA oversees the advertising.

DR. McGOWAN: Thank you. Dr. Bradley?

DR. BRADLEY: I think that prescription is actually quite important because this is the opportunity for the physician to actually speak to the parents or the patients. All of the comments about pandemic influenza being confused with seasonal can be addressed; the side effects of the drug; how bad the pandemic might be; how to access information when a pandemic comes so that you know that the pandemic is actually here. All of those things I think will

be key features of a physician-patient interaction at the time that the prescription is written that you might not get if it was OTC.

DR. McGOWAN: Thank you. Tracy?

MS. SWAN: I am just thinking about how this really plays out in my real world. When I go to my pharmacy I get something shoved in my face to sign, before they will give me my prescription, saying that I have already received counseling.

So, sort of relying on doctors who may be overburdened, nurses who may be overburdened or pharmacists who may be equally overburdened might not be the best case, and I think this is going to wind up behind the counter for the very reason that people are going to steal it if they need it and they can't afford it.

So, why not do an operational study where pharmacy staff, not just the pharmacists, get trained with some basic information or questions to ask people, do you understand? Tell me what a pandemic is? Are there children in your household? And, this becomes sort of a normal part of the pharmacy encounter because if we have a pandemic on our hands and we don't do this, it is going to be a nightmare,

but if it is routine it will make things easier for everyone.

DR. McGOWAN: Thanks, Tracy. Dr. Brass?

DR. BRASS: First of all, I think it is important, I think drugs are confused, treatment or access during a pandemic versus stockpiling. I think during a pandemic any stores will be rapidly depleted and it is the stockpiling that matters, not the acute access during a pandemic.

Second, I am officially an agnostic in the absence of data whether OTC is appropriate, but I share Dr. Bradley's concerns and amplify them because repeat visits are an opportunity to reinforce those messages, reassess appropriateness, do the initial screening and reassess the screening and educate.

Finally, I also think in that context there is a Ause it or lose it@ characteristic to this product. If somebody spends money and it is near the expiration date, their tendency to use it for non-pandemic indications is going to increase.

This is why I alluded to earlier about whether there is going to be purchase in the context of the consumer research trials because consumer purchase is a huge co-

variate in determining consumer behaviors in the trials and in the real world. So, I think that, again, the ongoing physician interaction to offer the opportunity to trade it in near the expiration date will minimize that as well.

DR. McGOWAN: Dr. Lipsitch?

DR. LIPSITCH: No.

DR. McGOWAN: Any remaining comments, thoughts, questions? Yes?

DR. HEWETT: Yes, one final comment and this echoes other related comments on disposal. Going forward, I would like to see that the packaging indicates clearly what to do with expired drug.

For example, I would imagine it wouldn't be prudent to flush it down the sewer system so that, although remote, wildfowl or domestic poultry could drink from it and maybe potentially develop resistance from that drug. Further, I would like to see studies to find out exactly what the consumer would do, when asked, on disposing the drug. I would like more on that going forward.

DR. McGOWAN: Dr. Neill?

DR. NEILL: Dr. Brass, reconcile for me, and maybe this is inherent in your Ayes, if@ missing button response

earlier, on the one hand, the knowledge that I can today write a prescription for my patients for the purposes of stockpiling, and do it badly without the proper information on time of use, etc., or programs that are available, much less all of the public brouhaha need for information at the time, reconcile the fact that I can do that now with our combined committee votes earlier, 20-6, that MedKits ought not be available for stockpiling and then subsequently this concern about stockpiling versus acute availability in a pandemic setting.

DR. BRASS: You are correct. So, you asked me to go back to my question 2 vote. It was the Ayes, if.@ As I said in my very earliest comment, I think the potential individual health, and maybe less public health now but the individual health benefit that is potentially substantial when you start talking about a 50 percent mortality rate for infection. It doesn't take very much individual exposure to get a particular individual benefit.

So, my Ayes, if@ was specifically centered around the consumer trials being done in a way that truly optimize and I thought the current setup did not.

DR. McGOWAN: Dr. Farber?

DR. FARBER: Just to clarify one thing that Dr. Neill just said, what I heard around the room in terms of the Ano@ votes wasn't no, we don't want the MedKits. It was no, we don't want the MedKits now because we don't have enough data to make sure that they are going to be safe and efficacious and that we need to do more studies. So, I don't think people were saying definitely no to the MedKits. I, personally, was not saying no to MedKits.

DR. NEILL: I asked the question not because I heard that but, rather, because my perception of reality on the ground, again, conveniently absent data, is that there has been stockpiling occurring. There are concerns about inappropriate use, and the kinds of systems that we may put into place or could improve upon by virtue of appropriately designed labeling, comprehension, selection, actual use studies, which I think are all necessary, could be improved and moved forward from where we currently stand.

I would never argue that we don't need more data, only that we are not deciding whether to move forward. That is happening. You know, we are doing it now. We are stockpiling now. We are just doing it really badly.

DR. FARBER: Yes, and I would agree with Dr.

Bradley that, you know, one of the things that we need to do is to ensure that there is physician input so that patients do get the message about how to appropriately use the medications and MedKits.

DR. McGOWAN: Dr. Havens?

DR. HAVENS: My response to both of you would be that moving towards an OTC indication allows a reasonable response to both of these issues, and the education issue can be addressed really at the time of influenza vaccine for example, or there are other methods to address the issue of patient education and how to do it.

As you point out, physicians are already in the middle. The number of times I have been asked for prescriptions is large, and we want to get out of the middle of that. The MedKit is one way, but perhaps imperfect for a variety of reasons we have heard today, and the OTC option would allow for a different approach that might answer many of those issues that you both bring up.

DR. McGOWAN: I think Dr. Good would like the last comment or question. No, you wouldn't? Marc?

DR. LIPSITCH: Thanks. Just briefly, the issue of over-the-counter versus prescription may be controversial

but relatively small, I would guess, when there is not a pandemic. But in the setting, assuming it is over-the-counter now and it will be over-the-counter in the setting as a pandemic as well, that might be a very good thing because it would allow faster access for the reasons that were mentioned.

Also, if I had no morals I would put some money in a pandemic. I would go and buy as much as I can and sell it at a profit. There are all sorts of weird scenarios in a pandemic with OTC where there is no control over who needs it being the ones who get it. I think that is a much, much larger issue to think about, both for big pros and the big cons in a pandemic.

DR. McGOWAN: Dr. Birnkrant?

DR. BIRNKRANT: With regard to the over-the-counter issue, we would have to convene another advisory committee to discuss that issue just by itself.

DR. McGOWAN: Well, on that note I think we have come to the end of all our questions. I hope we have provided the FDA with significant input. I think we have been presented with a problem of immense significance and magnitude. I think it is definitely a work in progress.

I think although the committee didn't vote in favor of rolling out MedKits, I think the consensus seems to be that the modifications, the studies, additional studies are not huge by any stretch of the imagination. I think that moving forward in a collegial fashion we can probably make a lot of progress in this direction.

I would like to thank everyone for their participation, the questions and comments, and call the meeting to a close. Thank you.

[The meeting was adjourned.]