UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEETING

Silver Spring, Maryland

Friday, December 14, 2007

PARTICIPANTS:

Committee Members:

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EDWARD B. NELSON, M.D., PH.D.

P R O C E E D I N G S

(8:00 a.m.)

DR. TINETTI: Good morning, everyone. We will start the meeting. I'm Mary Tinetti, the chair of the Nonprescription Drug Advisory Committee. And I'm in the Department of Medicine at Yale University. And I'm going to read our opening statement.

"For 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 is that today's meeting will be a fair and open forum for 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. We look forward to a productive meeting.

"In the spirit of the Federal Advisory Committee Act and the Government in

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 the Severn room immediately following the meeting today.

"Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch." Thank you. We'll now introduce the members of the committee.

DR. NELSON: Ed Nelson, vice president of Martek Biosciences and I'm the industry representative.

DR. SHRANK: Will Shrank, a physician, and in the Division of Pharmacoepidemiology and Pharmacoeconomics at

Brigham and Women's Hospital and Harvard Medical School.

DR. TAYLOR: I'm Robert Taylor, professor of medicine and pharmacology, Howard University College of Medicine in (off mike).

DR. HONSINGER: I'm Richard Honsinger. I practice medicine in New Mexico. I'm on the clinical staff at the University of New Mexico.

MR. OWNBY:: Dennis Ownby. I'm a professor of pediatrics and internal medicine at the Medical College of Georgia in Augusta, Georgia.

DR. LEVIN: Arthur Levin, director of Center for Medical Consumers, the consumer representative.

DR. NGO: Lt. Cmdr. Diem-Kieu Ngo, DFO, designated federal official.

MS. HOFFMAN: Ruth Hoffman, executive director, Candlelighters Childhood Cancer Foundation, patient advocate.

DR. GRIFFIN: Marie Griffin, internist and pharmacoepidemiologist at Vanderbilt University.

DR. FITZGERALD: Garret FitzGerald, professor of medicine and pharmacology at the University of Pennsylvania.

DR. FOLLMANN: Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. D'AGOSTINO: Ralph D'Agostino, professor and chair of the Mathematics and Statistics Department at Boston University, biostatistician.

MS. LUMPKINS: Debbie Lumpkins, FDA, Division of Nonprescription Regulations Development.

DR. KOENIG: Michael Koenig, interdisciplinary scientist in the Division of Nonprescription Regulation Development with FDA.

DR. JOHNSON: And Susan Johnson, associate director, Office of Nonprescription

Products.

DR. GRIFFIN: Good morning. I would first like to remind everyone present to please silence your cell phones if you have not already done so. I would also like to identify the FDA press contact, Ms. Rita Chapell. If you're in the room, please stand up. I think she is running late in traffic, so she'll be here a little bit later. I would like now to read the conflict of interest meeting statement.

"The Food and Drug Administration has convened today's Nonprescription Drugs Advisory Committee meeting under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the committee are special government employees or regular federal employees for other agencies or are subject to federal conflict of interest laws and regulations.

"The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC section 208 and section 712 of the Federal Food, Drug, and Cosmetic Act, FD & C Act, are being provided to participants today's -- in today's meeting and to the public.

"FDA has determined that members and consultants of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC section 208, Congress has authorized FDA to grant waivers to special government employees who have potential conflict of interests" -- I'm sorry, "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 FD & C

Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts who are necessary to afford the committee essential expertise.

"Related to the discussions of today's meeting, members and consultants of this committee who are special government employees 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 purposes of 18 USC 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 the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as OTC oral nasal decongestants. This is a

particular matters meeting involving specific parties.

"Based on the agenda for today's meeting and all financial interests reported by the committee members and consultants, conflict of interest waivers have been issued in accordance with 18 USC section 208(b)(3) and section 712 of the FD & C Act for Dr. Ralph D'Agostino.

"Dr. D'Agostino's waivers involve his membership in an effective firm's unrelated data safety monitoring board. He receives between $10,001 to $50,000 per year. The waivers allow this individual to participate fully in today's deliberations.

"FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/ohrms/dockets/default.html. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Office, Room 630 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. Dr. Edward Nelson is serving as the industry representative acting on behalf of all in the regulated industry and is employed by Martek Biosciences.

"We would like to remind members and consultants 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 advice the committee of any financial relationships that they may with any firms at issue." Thank you.

DR. TINETTI: Thank you. I just

wanted to remind everybody of one change in the agenda. The open public hearing time has changed to 1:25 p.m. due to last-minute changes to the agenda. And now we'll move on to the introductory remarks from the FDA by Susan Johnson.

DR. JOHNSON: Good morning. On behalf of the phenylephrine FDA team, I'd like to welcome back members who participated in yesterday's discussion of Mevacor and welcome participants who are joining us just for the day, including our pulmonary and allergy experts. We want to thank you all for helping us to consider and reconsider efficacy of phenylephrine as a nasal decongestant in the OTC marketplace.

In February of this year, we received a citizen petition that requested that FDA revisit the efficacy issues, specifically asking us to find that there are insufficient data to support the general recognition of effectiveness or GRAE status

that is required for efficacy inclusion in the OTC monograph.

We were also asked to require additional studies of safety and efficacy of higher doses of phenylephrine and to remove pediatric dosing recommendations from the OTC monograph.

We'd like to advise the committee that the focus of this meeting needs to be somewhat limited in order to make this a manageable project. So what we're asking the committee to consider today is the effectiveness of phenylephrine for the symptomatic treatment of nasal congestion either related to the common cold or upper respiratory allergies, which are the monograph indications.

We're asking the committee to focus on patients aged 12 years of age and older and to look at oral dosing of immediate release formulations, which are those formulations included in the monograph.

Phenylephrine, in the monograph, includes two salts, the hydrochloride and the bitartrate. And you'll be hearing more about those formulations later today.

We're specifically excluding for the committee a discussion of the pediatric oral dosing of phenylephrine. And the reason for that is that there was an October advisory committee which discussed cough, cold product use in pediatrics at length. And FDA is working to facilitate quickly final recommendations for pediatric dosing using the FDA's committee at that time's advice. We're also not including the monograph topical nasal dosing. And we're not looking at non-monograph dosing, such as, oral dosing under NDA formulations.

You'll hear today about multiple sources of data and analyses. You'll be hearing about the OTC drug review which prompted the monograph, including the advisory panel that reviewed an initial set

of data. You'll be hearing about a meta-analysis from the petitioner and another one submitted by the Consumer Healthcare Products Association. You'll also be hearing about studies that were conducted by Wyeth Consumer Healthcare and studies conducted by Schering-Plough Healthcare.

Primary aspect of today's discussion is the use of various congestion or decongestion metrics. The first metric that you'll be hearing about is one that was popular, more prevalently used in the '60s and '70s when the panel was doing its review, Nasal Airway Resistance. This is an objective assessment of airway patency. And while it is less frequently used in trials these days, the correlation with symptom score research continues to be ongoing.

You'll also be hearing about symptom scores which are subjective. They're required for approval of NDA products by the FDA because we feel that they reflect patient

experience and are more amenable to labeling considerations. For the agenda today, FDA will be presenting the background of the OTC drug review followed by efficacy and a limited amount of safety data. We won't be asking the committee today to make a risk benefit assessment.

We'll be talking about statistical evaluation, particularly of the meta-analyses and the use of clinical endpoints. The FDA presentations will be followed by a presentation by the petitioner and colleagues and industry presentations from CHPA and Schering-Plough.

And finally, we'll be asking NDAC and other members, which aspects of the data presented, if any, support the efficacy of phenylephrine. We'll be asking you to consider what conclusions you draw regarding the dose and dosing of phenylephrine and what, if any, additional studies you recommend. Thank you. Dr. Tinetti.

DR. TINETTI: Next, Mary Robinson.

DR. ROBINSON: Good morning. I am Mary Robinson with the Division of Nonprescription Regulation Development, Office of Nonprescription Products. I am going to give a brief overview of the OTC drug review history of phenylephrine leading up to the present.

In January 1972, the OTC drug review was initiated to ensure that OTC drug products were safe and effective. Approximately, 800 active ingredients in OTC marketed drug products have been reviewed. At the beginning of the OTC drug review, FDA divided the active ingredients in OTC marketed drug products into 26 therapeutic categories and determined that the drug review would be a three-step process.

In the first step, the advisory review panel reviews and evaluates data submitted in response to the call for data notices. The panel's findings and

recommendations are published in an advance notice of proposed rulemaking. Step 2 is FDA's tentative review of the panel's report and evaluation of public comments submitted in response to the ANPR. Upon completion of the review, a tentative final monograph is published in the form of a proposed rule. In step 3, FDA reviews updated literature and comments submitted in response to the TFM. These comments may include new data, objections, or a request for oral hearings.

This process culminates in the publication of a final monograph to establish regulations in the code of federal regulations. FDA established 17 independent advisory review panels. Each panel included voting members and non-voting members. The advisory review panel on over-the-counter cold, cough, allergy, bronchodilator, and anti-asthmatic products was the panel that reviewed phenylephrine hydrochloride.

The panel was first convened in

November 1972. This panel met for 2-day working sessions approximately 24 times from 1972 to 1976. The panel defined nasal decongestants as agents that reduce nasal congestion in patients with acute or chronic rhinitis. Nasal decongestants can be administered topically as drops, sprays, or inhaled vapors or orally in a solid or liquid dosage form.

Phenylephrine hydrochloride and pseudoephedrine were the only active ingredients considered as both oral and nasal decongestants. The panel was charged with making recommendations based on their experience and the available data to establish conditions of use with respect to dosing, directions, warnings, and in some cases, testing and final formulations.

The panel was charged with applying effectiveness standards in accordance with 21 CFR 330.10(a)(4)(ii), which states, "Effectiveness means a reasonable expectation

that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed."

The panel was also charged with classifying active ingredients in one of three categories. Category 1, generally recognized as safe and effective for the claimed therapeutic indication. Category 2, not generally recognized as safe and effective. Category 3, insufficient data to determine safety and effectiveness. Phenylephrine hydrochloride was classified as category 1 at a dose of 10 milligrams every 4 hours not to exceed 60 milligrams in 24 hours.

After the panel completed its deliberations in September 1976, the FDA published in the advance notice of proposed rulemaking for cold, cough, allergy,

bronchodilator, and anti-asthmatic products the panel's unaltered conclusions and recommendations for the monograph on OTC nasal decongestants. That monograph included phenylephrine.

Following the publication, the FDA allowed a comment period in which any interested party could submit information regarding the panel's recommendations and conclusions, submit new data, and reply comments. Following the comment period -- sorry, I must have skipped a page, okay. Following the comment period, FDA reviews and evaluates the ANPR recommendation, public comments submitted in response to the ANPR, reply comments, new data, and scientific literature, if any.

One comment questioned the panel's findings of effectiveness of phenylephrine hydrochloride based on heterogeneity of the findings among the studies and overall strength of the findings. FDA concluded that

evidence to support phenylephrine hydrochloride was sufficient based on the studies, information on clinical use, marketing experience, and the panel's expertise. The agency's conclusions were published in the TFM on January 1985.

This proposal constitutes FDA's tentative adoption of the panel's conclusions and recommendation as modified on the basis of the comments received and the agency's independent evaluation of the panel's report and any new data. The TFM allowed a 120-day comment period for written comments and objection. This proposal also allowed a 12-month period for submission of data. No additional comments were received about phenylephrine hydrochloride.

In August 1994, FDA published a final rule to promulgate regulations that establish standards for labeling to be used in OTC nasal decongestant drug products. Manufacturers were given an effective date at

which time their drug product must be in compliance with the monograph. The final monograph is included in the code of federal regulations.

The final monograph includes phenylephrine hydrochloride as an active ingredient for the purpose of nasal decongestant with the allowable uses. One, temporarily relieves nasal congestion due to the common cold, hay fever, or other upper respiratory allergies. Two, temporarily relieves sinus congestion and pressure. And with the recommended directions, take 10 milligrams every 4 hours, not to exceed 60 milligrams in 24 hours.

A final monograph can be amended with the submission of a citizen petition. On March 2002, a citizen petition was received requesting that phenylephrine bitartrate in effervescent dosage form be generally recognized as safe and effective. However, it should be noted that

phenylephrine bitartrate was submitted to the OTC review. However, at the publication of the final monograph, data were insufficient to show effectiveness as a nasal decongestant. Therefore, phenylephrine bitartrate was non-monograph in the FM.

The citizen petition, however, contained information describing extensive domestic and global marketing history data along with an absence of significant safety concerns. The petition also included pharmacological -- pharmacokinetic data demonstrating that phenylephrine hydrochloride and phenylephrine bitartrate have comparable bioavailability profiles. Based on this data, the OTC nasal decongestant final monograph was amended in August 2006 to allow for phenylephrine bitartrate in effervescent dosage form.

This slide shows that there are other nasal decongestants included in the final monograph. Note that they are three

oral OTC nasal decongestants. The two pseudoephedrine active ingredients are currently sold behind the counter because of the use of these drugs to make illegal substances. They are also atopical drugs available for OTC use as nasal decongestants.

In February 2007, another petition was filed to amend the OTC nasal decongestant final monograph. The petition states that phenylephrine hydrochloride at the dose of 10 milligrams every 4 hours is not effective. Phenylephrine bitartrate at the dose of 15.6 milligrams every 4 hours is not effective.

The petition requests that the maximum dose of phenylephrine hydrochloride and phenylephrine bitartrate be increased. The petition also requests that FDA require additional studies to validate that a 25-milligram dose of phenylephrine hydrochloride is more efficacious than the 10-milligram dose of phenylephrine and is as safe. The petition contained a meta-analysis

of studies submitted to the ANPR. No new data was submitted in the petition.

Today, we are to hear the Nonprescription Drug Advisory Committee's view on the existent efficacy data for phenylephrine. The recommendations made by the committee will be carefully considered by FDA in the regulatory review process.

DR. KOENIG: Good morning. I'm Michael Koenig, an interdisciplinary scientist in the Division of Nonprescription Regulation Development, Office of Nonprescription Products.

Over the next 30 minutes, I'm going to review what we know about the effectiveness and safety of phenylephrine hydrochloride taken orally as an OTC nasal decongestant. I'm going to focus on what we know for two specific doses of phenylephrine hydrochloride, the 10- milligram dose currently recognized as safe and effective or GRASE and the 25-milligram dose suggested by

the petitioner as a potentially more appropriate dose.

As you've heard, phenylephrine bitartrate, in an effervescent dosage form, was added to the monograph in 2006 based on a similar bioavailability profile to that of phenylephrine hydrochloride. I am not going to review safety and efficacy data for the bitartrate salt. I'll begin by talking about the effectiveness of phenylephrine hydrochloride.

First, I will describe the 19 studies that were included in our current review. Thirteen of these were reviewed by the panel and were included in the advance notice of proposed rulemaking. And six additional studies have been added that we are aware of. I will then describe -- I will describe these studies generally and then describe the two endpoints, the objective and subjective endpoints, that were utilized to assess the effectiveness of phenylephrine

hydrochloride.

Finally, in this section, I will specifically evaluate the studies that demonstrated statistically significant effects or effectiveness at the 10 and 25-milligram doses of phenylephrine hydrochloride. Then, because we're interested in identifying an effective dose and dosing interval for phenylephrine hydrochloride, I will very briefly describe what we know about the pharmacokinetics of single dose phenylephrine hydrochloride.

Next, I will describe for you what we know about the safety of 10 and 25-milligram doses and considering the cardiovascular risks as well as adverse events that were identified both in the studies that were conducted as well as what's available in our adverse event reporting system or AERS database. I will then close with a summary of our findings.

Now, in your -- in the package that

you should have if -- should have a rather thick package of FDA presentations. If you'll go to the last page of my part of that presentation, following page 18, there is a handout that I would like you to refer to. Committee members received a copy of this handout last week, I believe, by FedEx.

And there is one change that needs to be made. If you're committee members and you're using that handout that you received last week, please make this change. On the study identified as Elizabeth 3, you should add an asterisk to the black box under the 25-milligram dose of NAR. So there should be an asterisk right here.

Okay, the handouts show you the 22 studies that we originally considered for this review. Three of these studies were excluded from the review for the reasons that are listed below in the footnote. And I'll just mention these to you quickly.

The first is a 1964 paper by

Blanchard and others. This study included a combination product that had an analgesic, and antihistamine, and a vasoconstrictor which we assume was phenylephrine hydrochloride, but that's not stated in the paper. In any case, there is no data specifically related to phenylephrine hydrochloride and its effects relative to placebo in the Blanchard paper.

We are also excluding the 1973 abstract by Rogers et al. This was a presentation apparently made at the 1973 meeting of the American Society for Clinical Pharmacology and Therapeutics. It has some information, some data but not enough to make any kind of statistically relevant conclusions.

And finally, we are excluding a 1971 paper by Hyrum Biekerman. We're excluding this one because this was primarily written -- the paper is a review of the technique, really, of measuring nasal airway

resistance. And the data comes -- that's relevant to this discussion comes from one figure. It's actually a table. And there is not sufficient information to make a statistical evaluation of that as well, data represented as means.

Now, still looking at the handout, as you see, all of the 19 studies that we are included are listed in the left-most column. And then if those studies were included in the advance notice of proposed rulemaking, there is a solid black block in the -- in that column. So you can see that there were all of the studies that were included in the ANPR.

You can see, in the column next to that, the eight studies that were included in the citizen petition. And in the column to the right of that, the seven of those same eight studies that were included in the meta-analysis conducted by the Consumer Healthcare Products Association.

Now, if you'll focus on the study that I've identified as Elizabeth 2, this is the second study conducted at the Elizabeth biochemical laboratories. You can see that this particular study was included in the ANPR as well as in the meta-analyses prepared by both the petitioner and by the Consumer Healthcare Products Association. Reading to the right further, you can see that all of the patients had a common cold. And as you'll see, this was a condition that was prevalent in many of these earlier studies.

You can also see that both endpoints, that is reduction and NAR -- sorry, nasal airway resistance and improvement in symptom relief were evaluated in this study, furthermore, at the 10-milligram dose as well as the 25-milligram dose. The presence of an asterisk next to these blocks indicates that there were statistically significant effects in that particular study.

So now to focus specifically on the 15 studies. There were 15 studies that the panel looked at. These were conducted between 1959 and 1975. As I've already indicated, we excluded the paper by Blanchard and the abstract by Rogers et al, leaving us with 13 studies. I've enclosed studies conducted at these four sites in a red box to indicate that these were all pretty much done together.

Those of you who have looked through the study information will probably recognize these as memoranda from N.A. Homi because most of these involved and were organized by the Sterling-Winthrop Research Institute. In addition to these studies, there is a paper published by McLaurin in 1961, and a paper -- and a study that was conducted, the primary investigator was Burton Cohen. This is the way that the -- you may see this referred to in the CHPA background package, Cohen, 1975. The study

was conducted by Bio-Evaluation, Incorporated.

In addition to the 13 studies that we included from the panel, we've added six. These were conducted between 1967 and 2007. These include a paper by Cohen published in 1972 and it's the same Cohen who was the primary investigator in that BEI study, three submissions which were previously unpublished from the Wyeth Consumer Healthcare organization. These studies were conducted between 1967 and 1983.

And two studies submitted recently. This first study submitted by a Schering-Plough organization was submitted with the petition and was conducted in January of 2006. I want to point out that we have included it in our studies even though it's a 12-milligram dose. This is the dose approved in the European Union. But just be aware of that. And then there is a more recent study just published, I think, week

before last or maybe last week in the clinicaltrials.gov, also from Schering-Plough in conjunction with Merck. This study was actually conducted in January-February of this year.

In general, I can describe the study characteristics for you. Again, we looked at 19 studies. Of those, 18 were specifically cited as randomized. We have every reason to believe that all 19 were, but one didn't say it was. Seventeen of them were double-blind. Eighteen of the studies were placebo-controlled, eight of them had an active control as well.

In terms of design, the majority were of the crossover type, meaning the same patients were exposed to the placebo and to the active drug. And four were of the parallel type, meaning different groups of patients were exposed to the different treatments. By far, the most -- most of the studies were single dose. There were two

multi-dose studies in which subjective studies were done. The doses tested ranged from 5 milligrams in one study to a maximum for effectiveness of 75 milligrams in one study.

Most of the studies, 16 of the 19, evaluated the 10-milligram dose. Ten evaluated the 25-milligram dose and seven evaluated both the 10 and 25-milligram doses in the same study. The number of patients tested per dose ranged quite a bit from a low of five patients in one study at a dose of 20 milligrams phenylephrine hydrochloride to one of the Schering studies, which was a parallel study, it included 126 patients in the treatment arm.

Most of the studies had fewer than 20 patients. In fact, talking to the statistician the other day, our statistician, that's actually probably more likely fewer than 16. Seven of them had 20 or more. All of the studies were done with adults

primarily. There were two studies that included adults over the age of 75.

And with respect to children, which I know we're not discussing today, I would just like to point out that there was one study in which the range of ages was listed as three patients in the 10 to 19-year-old group. So we have at least one study that has been reported actually as an 8-year-old participated but only three.

Patient condition was common cold in most cases, cases. Also allergy and seasonal allergic rhinitis.

Two cases of upper respiratory tract infection, that is, two studies in which the patients had upper respiratory tract infection. One study had a variety of conditions and these are noted in footnote 5 of your handout. And in one study, actually, the one conducted originally in 1959 by Sterling-Winthrop, the patients were quoted as being apparently healthy and not

congested. So it may not be surprising that this is not one of the studies that demonstrated the effective decongestion.

The origin of the condition ranged from naturally occurring in 17 cases to the two Schering-Plough studies in which the condition was induced by exposure to pollen in an environmental exposure unit or chamber. Now let me discuss briefly the two endpoints that were used.

One of these was an objective endpoint measuring nasal airwave resistance or NAR. This gives an idea, as you heard Dr. Johnson say, of the openness or patency of the airway. Objectively, this was utilized in 17 of the 19 studies and it was the only endpoint in four of the studies.

The subjective measure of how people felt after being treated with placebo or an active drug phenylephrine was utilized in 15 of the 19 studies and was the only endpoint in the two Schering-Plough studies.

And then both endpoints, that is, reduction in NAR as well as symptom scores, were used in the same study and 13 of the studies we looked at.

So what is this nasal airway resistance? Well, congestion or swelling of the nasal mucosa obstructs the nasal cavity making it more difficult, if you will, for air to flow through the nose. So nasal airway resistance under congestion -- under conditions of congestion is increased. Air doesn't flow as freely through the nose.

Decongestion then is the process by which nasal airway resistance is decreased by opening the airway by reducing the swelling of the nasal mucosa. This is done by the vasoconstrictor action of phenylephrine hydrochloride. So what you're going to see, as we look at the effectiveness data in terms of NAR, if it's effective, is a decrease in nasal airway resistance.

NAR is measured by a process

referred to as rhinomanometry, sometimes just simply referred to as rhinometry. This is a measurement of airflow and pressure within the nose during respiration. Process has been in use for quite a long time. It actually surprised me. This is not a misprint; it should be 1894. And it's been widely used -- very widely used in the 1960s and '70s during the time that the panel was reviewing the data.

It is still used today and there are some very staunch extensively published proponents of this method including Ronald Eccles at the Common Cold and Nasal Research Center at the Cardiff University in Wales in the UK, who has actually made some comments about this phenylephrine question, and Michael Schumacher at the University of Arizona Health Sciences Center in Tucson. So it's not like Latin; it's not a dead language. It's still going on.

One thing that we noticed as we

looked through these studies, specifically at studies evaluating effectiveness by looking at NAR, was that there was no particular standardization. Or put another way, there was a fair amount of heterogeneity in the way the studies were conducted. They were based on different methods.

Some of the earlier papers referred to a method that was published in 1936 by Sternstein and Schur. Others refer to the method of McLaurin and still others refer to other methodologies. Furthermore, the place at which NAR was measured, that is, anterior, in the front part of the nose or posteriorly in the back of the nose, differed in these studies.

Anterior is the more commonly used method, I understand, today. Many of the studies utilize different instruments. Some of the earlier studies conducted by and for the Sterling-Winthrop research labs used a Butler-Ivy instrument. And other papers --

other studies actually talked about trying to make modifications and testing their modifications as part of their experiment. The studies submitted by Wyeth used a Respiron instrument.

We don't have any information in the studies that we have about whether these machines were calibrated, how often they were calibrated, the competence of the technicians that operated them. And so there are some issues there.

In terms of evaluating NAR, NAR was evaluated over different time courses ranging from 1 hour post- administration to 5 hours post-administration and within that time course, at different time intervals. Typically, within the first hour, NAR measurements were made every 15 minutes, and then every half-hour in the second hour, and then every hour. But there was one study in which the gap between the second time point and the third was 3 hours. That's between 2

and 5 hours.

And finally, there were different numbers of replicate measurements made at each time point. Sometimes there were five; sometimes there were four. Sometimes it was nostril; other times it was both.

Now the subjective measurement of symptom scores relies, as I said earlier and you heard Dr. Johnson mention, on the patient's subjective evaluation of their feeling of the relief of symptoms.

This was done, typically, using an ordinal scale and this usually ranged from four to six points. At least 10 of the studies that we looked at used a 5-point scale, such as I'm showing here, ranging from zero, which a patient would record if his nose -- his or her nose felt completely clear, to a maximum on this 5-point scale of 4 if the nose were completely blocked.

Now effectiveness in terms of a symptom score would, like the NAR, be a

decrease. That is, you would hope to see -- if it's working, you would hope to see a drug cause the score to go from a high score to a lower score.

So now, let's look at what we've got for data. And again, I'm focusing on the 10 and 25-milligram doses. For the 10-milligram dose, there were a total of 16 studies. Fourteen of these evaluated reduction in NAR and seven of those 14 demonstrated a statistically significant reduction at one or more time points following the administration of phenylephrine hydrochloride at a 10-mg dose. Twelve studies included a measure of symptom relief. And in five of those 12 studies, symptom scores were significantly improved over the course of the experiment.

At the 25-milligram dose, there were fewer studies. A total of 10 were conducted at this dose. Seven of the 10 studies that evaluated NAR showed a

statistically significant reduction in NAR. And of the eight studies that evaluated symptom relief at the 25- milligram dose, three showed statistically significant improvement in symptom scores.

And now, looking more specifically at the studies that did demonstrate statistically significant effects. The studies that are shaded in blue were available to the panel and presumably were -- and were included in the panel's review. Those in white down here, not shaded, are ones that we've added to what the panel saw. You can see that the number of subjects range from a low value of 8 in this Wyeth study to a maximum value in these studies of 100.

I should point out that this -- I've got 25/100 because 25 studies patients participated in a parallel study evaluating NAR and those same 25 patients were included with 75 other studies patients in a review of subjective scores of symptom relief. So

there were a total of 100 patients in the subjective evaluation of effectiveness in this case.

All but one of the studies was placebo- controlled. That was the Wyeth study, G1-A. They referred to changes relative to the baseline. Three of the eight studies utilized active controls, ephedrine or phenylpropanolamine. And in the next column, I capture or try to capture the onset of effectiveness.

This is the first time point at which we see a statistically significant effect. And this ranged from 15 minutes or a quarter of an hour to as long as 90 minutes or 1-1/2 hours. In the column to the right, I'm trying to demonstrate in some studies that weren't set up to do this how long the effect lasts by measuring the last effective time point relative to the total observational period.

What you can see is, if the total

observational period is only 2 hours, the last effective time point is at the end of that 2 hours. So we know it's at least 2 hours. And cases where the total observational period is 4 hours or more, we get values that are as high as 3 hours at which the phenylephrine hydrochloride, 10 milligrams, is still demonstrating a significant effect.

In terms of reduction of NAR, these are the P values in these two cases. This one at Cohen 72 and this one at Wyeth 4010, you see multiple P values because P values were reported for each time point, and ranged in these two experiments, and were not consistent throughout.

I would like to point out that in this multi- site study done with Wyeth 4010, only one of six sites containing 12 subjects actually looked at NAR. The other five did not look at NAR, but that one site did and found a statistically significant

effectiveness of 3 hours over a 4-hour time period.

In terms of symptom relief, again, five of these studies showed significant symptom relief. Two did not. The -- all six of the studies in this Wyeth multi-site study did conduct symptom relief measurements. And in those all five of the six showed not significant changes. So overall the effect is not significant.

Now, looking at the 25-milligram dose, again, seven studies show statistically significant effects. One thing I would point out is that, and because it's going to come up later in Dr. Lin's presentation, all five of the Elizabeth Biochemical Laboratory studies demonstrated statistically significant effectiveness at the 25-milligram dose.

In addition, the panel included the Cintest 1 study that proved to be effective and we have added the Cohen 72 study. These

studies are also small ranging from a low value of six subjects in Elizabeth 2 to a maximum of 16 studies -- patients in Cohen 72. All were placebo- controlled. Five of the seven had active controls.

Onset for the 25-milligram dose also began as early as 15 minutes or a quarter of an hour, and in one case, took as long as 2 hours to become effective. In terms of last effective time point, again, we see effectiveness for at least 3 hours and some suggestion that there may actually be greater than 3 hours over the course of the experiment.

Again, these refer to multiple P values. And finally, you can see that only three of these studies did the symptom score significance correlate with the objective score reduction in NAR.

And now, again, because the effective dose and effective dosing interval will depend, in part, on pharmacokinetics, I

want to go through very briefly what we know. Really, there hasn't been until recently -- and I found this in the Schering-Plough background material. There hasn't been a great deal done as -- again, looking in the literature, since about 1993 when a couple of review papers appeared.

But basically, the absorption is complete. The oral dose of phenylephrine hydrochloride is -- results in a bioavailability of about 38 percent. This is a figure that we've had since a 1982 paper by Hengstmann and Goronzy, and this is relative to the IV dose. I believe Dr. Hendeles is going to talk about this in his presentation as well.

The time, or the concentration, or maximal concentration in the plasma shows a fair amount of variation. And I'd just like to summarize briefly for you what that is because that may hinge, of course, on bioavailability.

In terms of total phenylephrine, that is, phenylephrine and all of its conjugates, some studies were done back in 1963 and 1964 and reviewed by Kanfer in 1993. A 9-milligram oral dose of phenylephrine hydrochloride, tritiated phenylephrine hydrochloride produced a Cmax ranging from about 200 to almost 300 nanograms per mil.

More recently, just a couple of years ago, a Schering-Plough study of pharmacokinetics with the 10- milligram dose came up with a Cmax of, I'm going to say, approximately 60 because I have the graph. I don't have the actual data. This is -- this was in the briefing materials that the committee members received.

Now, compared with the total amount, that is, phenylephrine and all of its conjugates, with just the parent compound, which, according to Schering, is the only active molaity.

Twenty-five years ago, when

Hengstmann and Gorozny did their experiment with a 1-milligram oral dose, they came up with a 0.9 nanogram per mil Cmax for the parent compound, quite a bit less than the 200 to 300 that were reported. And I know that's a higher dose but considerably less than the total, which is what we were working off of for quite some time. In the Schering-Plough study with the 10-milligram dose, the effect is approximately or the Cmax is approximately 0.6 nanograms per mil.

So one thing that's very interesting is, and I'm sure you'll hear more about this in the Schering presentation, the Cmax can differ by a factor of 100 depending on whether you consider phenylephrine and all of its metabolites or just phenylephrine, free phenylephrine, if you will, parent phenylephrine.

The time to maximum concentration in the plasma is about an hour. Earlier studies looking at total phenylephrine

including metabolites ranged from 1 to 1.33 hours. Earlier study with the parent phenylephrine or free phenylephrine was about 75 minutes or 1-1/4 hours. The Schering study that's included in the briefing materials is something on the order of about half an hour.

Distribution. The serum levels of phenylephrine hydrochloride decline rather quickly and mono- exponentially as opposed to the bi-exponential decline seen with an IV dose. There appears to be or there is reported to be minimal penetration into the brain, and there is almost no data or there is no data on protein binding. Metabolism takes place almost exclusively in the gut wall and in the liver, primarily forming sulfate conjugates.

As you may know, there is some deamination by monoamine oxidase and some glucuronidation occurs as well. And then in terms of excretion, excretion of the parent

and metabolite phenylephrine compounds is in the urine almost exclusively. The elimination half-life is about 2 to 3-1/2 hours.

And now I'll look very briefly at safety, what we know about the safety of the 10 and 25-milligram doses. Our main concerns are the increase in blood pressure that is characteristic of sympathomimetic drugs. It operates, as we've said, by -- as a vasoconstrictor shrinking the swollen mucosa. I would also point out that phenylephrine hydrochloride is GRASE or, again, generally recognized as safe and effective for the OTC treatment of hemorrhoids, shrinking of hemorrhoidal tissue.

And perhaps because of that increase in blood pressure, there is a reflex decrease in pulse rate, bradycardia. And this appears to be done by a compensatory action of the vagus nerve. So as blood pressure increase, the vagus stimulates the

heart to beat less rapidly.

This is a paper at a very high dose, oral dose of phenylephrine hydrochloride. This was actually the first reference in the section of the ANPR dealing with phenylephrine hydrochlorides written in 1941. I wasn't even born yet. This was a 250-milligram dose and that's hard to believe. 250-milligram dose, again, given orally to seven patients. And what you can see is at this very high dose and this is just a profile for one patient of seven with the initials N.D., blood pressure increases -- systolic blood pressure increases quite a bit, in fact, by a factor of about -- it goes up by about 45 millimeters of mercury over about an hour period.

Diastolic blood pressure is also increased at the same time by about 30 millimeters of mercury and there is this compensatory decrease in pulse rate. For this patient, that amounted to about 28 beats

per minute. Rather robust. We're not going to be looking at 250 milligrams.

We are going to be looking at 10-milligram and 25-milligram doses. And what we saw is that in the studies that had evaluated blood pressure and pulse rate, the results overall were very inconsistent. By far, most of the studies reported no significant effects in terms of any of these cardiovascular parameters. And where -- very often, where we saw a significant increase in a parameter, another study would report a significant decrease.

If it was an increase in systolic blood pressure or diastolic, they always seemed to be about -- they were less than about 5 millimeters of mercury. So if you keep in mind that that 250 produced 40 millimeters, that's a lot less. The decreases in blood pressure were typically less than 3 millimeters of mercury. And significant changes in pulse rate were

typically no more than 11 beats per minute up or down.

At the 25-milligram dose, a very similar pattern. Again, most of the studies, at least in terms of blood pressure, reported no significant effects. There did seem to be a little bit more activity in terms of pulse rate significance, but again, up and down. When investigators commented in their summary of the data, they typically said that the effects were minor or moderate or they often said of no clinical significance or not clinically relevant.

So in terms of adverse events that were reported during these studies, none were reported at all in six of the 10 studies that reported adverse events at the 10 or 12-milligram dose. And in one of the two that was reported adverse events, only one reported that there were any significant or that there were any adverse events.

Most of these were described as

minor, moderate nuisance. They did not seem to be of any great concern to any of the investigators at either the 10 or the 25-milligram dose. Schering-Plough does report two severe AEs occurred during the 8-hour post-treatment observation for the study conducted this year. And -- but I don't have the specifics about what that was.

Now, in collaboration and in consultation with colleagues in our FDA Division of Drug Risk Evaluation and the Office of Surveillance and Epidemiology, these folks conducted a search of our adverse event reporting system or AERS database over the period of 1969 through October 3rd of the this year.

They identified 26 unique cases of adverse events in the general population associated with orally administered, single ingredient phenylephrine. So we asked them to exclude all of the combination products that may have included phenylephrine.

In these 26 cases, they reported four serious cases. One of these was a death. This was an intentional suicide due to an overdose on a number of different drugs including phenylephrine hydrochloride. It seems to -- the others were hydrocodone and chlorpheniramine. And most of the evidence suggests that the death was probably due to hydrocodone in that case.

There were three hospitalizations. One was a 44-year-old female who had hemorrhagic stroke. We don't know how much phenylephrine she took or when she took it relative to the adverse event. There was a 15-year-old male who had elevated blood pressure. But this was later attributed by hospital staff to glomerulonephritis and not to the single dose of phenylephrine hydrochloride he had taken.

And finally, there was a 13-year-old male with paralysis and a depressed level of consciousness. This was

attributed -- his condition was attributed by two different emergency rooms to illicit drug use and he was released. And in any case, the 6-day time course of his adverse event was considered to be too long for the single dose of phenylephrine he had taken.

There were 13 cases involving an overdose. Five of these were due to medication errors. And this was typically people following the dosing instructions for Sudafed, which is pseudoephedrine, while they were actually taking Sudafed PE, which is the phenylephrine hydrochloride dose form.

Now, to very briefly and quickly summarize, let me just start with effectiveness. Again, we -- in terms of effectiveness, there were two endpoints that we evaluated or that we reevaluated. In terms of reduction in NAR at the 10-milligram dose, seven of the studies -- seven of the 14 studies that evaluated NAR produced statistically significant effects. And at

the 25- milligram dose, seven of the 10 studies that evaluated NAR showed statistically significant effect.

And in terms of symptom scores, significant symptom relief for the 10-milligram dose, five of 12 showed statistically significant improvement in symptom scores. And the 25-milligram dose, three of eight showed statistically significant improvement.

Very quickly, with pharmacokinetics, that 38- percent figure that we've used since 1982 for bioavailability may be too high. Cmax has been reported as ranging from 60 to 300 nanograms per mil for the total phenylephrine and all of its conjugates and is about a hundredfold lower or more for the parent phenylephrine compound.

In terms of the time to reach that concentration, it looks like it's about an hour although there is that one study showing

that it can occur as early as half an hour. And elimination, again, is primarily in the urine with a half-life of 2.1 to 3.4 hours.

In terms of safety, we, overall, see inconsistent effects on systolic and diastolic blood pressure and pulse rate. Majority of the studies showed no effect. And in terms of adverse events that were reported with the studies, these were classified by the investigators as minor, or moderate, or of the "nuisance variety". And that's a quote.

And in terms of safety with respect to the AERS database, there were a total of 26 cases over the 38-year period from 1969 to 2007 but -- for a single ingredient, orally dosed phenylephrine. But these did not exclude samples in which other drugs were taken besides phenylephrine. There was one death, but that was not attributable to phenylephrine. And there were three serious cases.

I'd like to just very briefly acknowledge the effort of our review team because these folks really did a great job putting -- helping me put this together. Thank you very much.

DR. TINETTI: We will have questions after the next --

MR. LIN: Phenylephrine citizen petition. I will provide some comments on the statistical evaluation of the effectiveness submissions.

Good morning. My name is Stan Lin. I am an associate director in the Division of Biometrics IV, Office of Biostatistics. PEH, short for phenylephrine hydrochloride and its 10 milligram effectiveness. The submissions I reviewed include two meta-analyses, the CP, the citizen petition meta-analysis and the CHPA meta- analysis.

The CP meta-analysis included eight studies as you saw. All of them were previously reviewed by the 1976 FDA expert

review panel. And in turn the CHPA meta-analysis included seven of the same eight studies included in the CP meta-analysis. In addition, the submissions I reviewed include two others. One is the EMC 140 which is a Wyeth Consumer Healthcare Report that included three previously unpolished studies conducted between 1967 and 1983.

In addition there was a clinical study conducted by Schering-Plough in 2006 as you have heard already.

This is a table that I adopted from Dr. Koenig's summary table. And you can see here the studies that were included in the expert review and the eight studies that were in the CP meta-analysis and the seven studies that were included in the CHPA meta-analysis. Now, these seven studies, they were all crossover in design. I guess they chose the seven because to give some homogeneity to the study design in their meta-analysis.

And note again, for the NAR, for

the 10 milligram, there were four red asterisks denoting statistical significant effect that the panel thought they had seen. I also note in this table for this one study Wyeth GIA and in Dr. Koenig's summary table there was a red star here. As you noted that was a baseline control study, so that statistical significance was relative to the baseline comparison. So I took the red star out of here because all of these were placebo-randomized single agent studies. Okay.

A very brief history, in 1976, the FDA published the events notice of proposed rulemaking in which the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products proposed PEH to be classified as GRASE, generally recognized as a safe and effective.

As we thought the panel reviewed a total of 13 studies and concluded that 4 -- this is a misprint, it should be 4. Four of

the studies I just saw in the last table, four of the studies demonstrated PEH 10 milligram to be effective in clearing the nasal airway, in other words reducing nasal airway resistance, NAR. The other studies did not show significant effect.

So now some comments on the CP meta-analysis. The citizen petition was based on a meta-analysis of some of the studies, the eight, particularly, previously reviewed by the 1976 advisory panel. However, the clinical effect in this -- endpoint use for the meta- analysis is the maximal reduction in nasal airway resistance which was measured periodically during the first 2 hours after administration of a single dose of 10 milligrams of PEH.

Use of this maximal reduction in nasal airway system is -- can be problematic. The endpoint was not mentioned in the studies reviewed by the panel, and so it was not the basis for the original design or analysis of

the studies included in the meta-analysis. It wasn't the secondary endpoint or secondary analysis, and it wasn't the primary analysis, for sure.

So use of this endpoint might obscure differences throughout the dosing interval. Again, this new endpoint is not appropriate to use for a reassessment of the effectiveness of a 10 milligram PEH. For example, if that was the endpoint, the trials could have been designed or might have been designed with -- sort of differently designed; for example the -- you measure more frequently so that you capture the maximal reduction more accurately.

Here are some generalities about meta-analysis. It is always a post-hoc reassembly or reanalysis of already existing data. And for sure it can be hypothesis-generating, but considered alone, rarely provides confirmatory evidence or its lack of without new data. And when you get down to

doing one of the -- one meta- analysis one issue of concern is the combinability of the results or the studies themselves. You will look for similarity in the study designs and also the data summarized. You will want them to be sufficiently homogeneous.

And my comment on the meta-analysis, of course, applies to either of the meta-analyses.

Now, here, I'm going to give some comments on this CHPA meta-analysis. As mentioned, it included seven crossover studies. The primary endpoint chosen for the meta-analysis was the reduction in nasal airway resistance in the first 60 minutes after a single-dose administration of PEH 10 milligram.

In the meta-analysis, evidence existed for a treatment-by-study interaction at different time points where the measurements were made. That indicates heterogeneity in the studies and/or their

outcomes and that potentially limits the poolability or combinability of data across the studies.

Looking at Dr. Koenig's presentation, I think that homogeneity might reflect the differences in the measurement method -- were used and some other differences in the studies.

Of the four studies which showed efficacy of the milligram, two of them were conducted at the same site, Elizabeth Biochemical Laboratory. As noted, the same laboratory also studied the efficacy of other doses of PEH.

Now, all the Elizabeth studies showed relatively stronger efficacy, whatever dose was studied, even though the studies were of very small size. And so averaging those studies with other studies because of their relatively strong demonstration of efficacy would mask a finding of no effect from some of the other studies. And looking

at the study themselves individually with limited replication of positive findings from the other sites, relative to the Elizabeth studies, the lack of multi- central representation of those small studies, limits the generalizability of its results.

So putting these two meta-analyses together -- and I have a summary and I believe that neither analysis is conclusive for the effectiveness of -- for the demonstration of the effectiveness of PEH 10 milligram. And I think that the CP meta-analysis did generate new hypothesis in terms of -- new analysis in terms of maximal reduction as an endpoint.

However, I believe its effect-discrimination properties, which gets into the assay sensitivity when used in a clinical study, needs to -- may need to be further evaluated, so that we can understand it better and we can design a study around it.

And once better understanding is done then new studies, of course, can be done in using that endpoint to evaluate effectiveness of NAR -- in terms of NAR over time.

I have just one more slide before I conclude my presentation. Remember, there were two other submissions that I reviewed. One of them was the Wyeth Healthcare Report, EMC 140; that study included three -- that report included three studies. The first one was a single blind; it had no placebo control. It had eight subjects on PEH 10 milligram. The second study was in eight subjects, eight-way crossover, and at the end of the study, no difference from placebo was demonstrated. As the previous presentation noted that the third study, AHR-4010-3 in -- by design in one of the six centers did measure NAR. It had 12 subjects, it did show significant difference in total NAR, between 30 and 180 minutes, but total NAR is not the

same as maximal error reduction.

And the other report that I looked at was a Schering-Plough study that was done in 2006. That was a 3-way crossover, single center, seasonal allergic rhinitis patients confined 6 hours in allergy chamber; and 38 of 39 subjects completed the study. At the end, again, no difference was shown when compared to placebo in the primary endpoints of symptom relief. And I noted -- I note that in the study NAR was not measured at all.

Okay, that concludes my submission -- I mean, presentation.

MR. WANG: Good morning. I am Xu Wang, a medical officer in the Division of Pulmonary and Allergy Products at FDA. I will be talking about clinical endpoints for nasal decongestants.

My presentation will cover the following three topics. First, nasal congestion and its pharmacological treatment,

and second, types of clinical studies for nasal decongestants, and finally, I will talk about assessment of nasal congestion in clinical studies.

I want to make this clear, my presentation reflects the division's current thinking and does not address the conclusions of the review panel, or the efficacy and the safety of phenylephrine. The purpose of this presentation is to provide information regarding how the division evaluates clinical studies of nasal decongestants.

As we know, nasal congestion is a predominant symptom of patients with common cold or allergic rhinitis. It is a subjective complaint usually reported by patients as stuffy nose, stopped-up nose, nasal stuffiness and a clogged-up nose. The management of nasal congestion may include environmental control, physical measures, surgical procedures such as removing polyps and a pharmacologic treatment. Here I will

talk about pharmacologic treatment only.

Pharmacological treatment of a nasal congestion includes topical and oral formulations. The citizen petition is about the effectiveness of phenylephrine as an oral nasal decongestant. OTC monograph oral nasal decongestants only include pseudoephedrine and phenylephrine. OTC monograph indication of a nasal congestion -- decongestants is temporary relief of nasal congestion due to common cold, hay fever, or other upper respiratory allergies, namely allergic rhinitis.

Two address the monograph indication I would like to further discuss clinical studies on the common cold and allergic rhinitis.

Clinical studies on the common cold can be conducted in naturally occurring and induced colds. In naturally occurring cold studies, volunteers are enrolled when they develop a naturally occurring cold. The

study subjects may comprise of a patient with a number of different cold viruses. In this type of studies enrollment is complete over a longer period of time.

In induced cold studies, volunteers are inoculated with a specified dose of a single-known cold virus. The study may be conducted with a shorter period of time. To support a nasal congestion indication the division expects to see the drug being tested in two naturally occurring cold studies, or one naturally occurring cold study plus one induced cold study.

Now, let's look at the clinical studies on allergic rhinitis. This study has included the following three types -- first, outpatient natural exposure, or real-life studies. These studies are conducted in patients with natural exposure allergic rhinitis. The study duration should be over 2 weeks for seasonal allergic rhinitis and over 4 weeks for perennial allergic rhinitis.

Second, "day in the park" studies; in this type of studies, subjects undergo a single-day exposure to allergies in outdoor setting. The study is affected by weather, relevant allergens, and season. Finally, environmental exposure units, or EEU studies, also referred to as chamber studies; EEU studies control energy and exposure in an indoor setting. It is a sensitive pharmacodynamic model. In general, EEU studies are used to further characterize the efficacy of a drug. EEU studies alone cannot support a nasal congestion indication.

These studies form a spectrum from outpatient to real-life scenario through the highly controlled model in an environmental exposure unit with "day in the park" studies fully in between. To support a nasal congestion indication, the drug should be tested in two outpatient natural exposure studies. "Day in the park" studies and EEU studies can be supportive, providing further

efficacy information such as onset of action and timing of the affect.

Now, I'd like to discuss the measurement to assess nasal congestion. That is, clinical endpoints for nasal decongestants. Clinical endpoints for nasal decongestants include nasal congestion scores, nasal airway resistance, and other objective measures such as nasal minimal cross-section area, and the nasal cavity volume. In this presentation I will only discuss nasal congestion scores and then nasal airway resistance.

These clinical endpoints maybe applied to any type of cold studies or allergic rhinitis studies that we have discussed. First, let's see the nasal congestion scores. Nasal congestion scores directly assess the presented symptom. I want to emphasize that. The symptom of nasal congestion is the OTC monograph indication of nasal decongestants. Nasal congestion scores

are usually rated on an ordinal scale.

There are two types of nasal congestion scores; they are reflective and instantaneous scores. Reflective scores measure the symptom severity over a predefined time period, assessing efficacy over the entire dosing interval. On the other hand, instantaneous scores measure the symptom severity at a time period preceding dosing to assess the efficacy at the end of dosing interval. Both patient self-assessed and the physician's rating of the scores can be measured. However, patient self-assessed nasal congestion scores are the division's preferred primary efficacy endpoints for nasal decongestant.

Now, let's look at nasal airway resistance, or NAR. NAR is a function of nasal airflow and Dr. Johnson and Dr. Koenig described earlier about how we measure nasal airflow. NAR is an objective measure of nasal patency. It has been used as one of

the outcomes to evaluate nasal congestions in clinical studies. Some investigators still prefer to use it as a major efficacy endpoint.

NAR provides valued efficacy information when it is positively correlated with the nasal symptom scores. From the previous presentations we see that in the majority of the studies that the panel reviewed, both NAR and the symptom scores were measured. It seems that NAR and the symptom scores responded to test drugs in the same direction in these studies.

Currently, the division accepts NAR as a secondary or supportive, but not a primary efficacy endpoint mainly, for following two reasons -- first, NAR does not directly assess patient symptoms. Also it does not directly address monograph indication for nasal decongestants, even though it is an objective measurement.

Second, in clinical practice NAR

may be discordant with nasal congestion. There may be several causes for this discordance including nasal cycling. Nasal cycling is the physiological phenomenon of alternating congestion and decongestion in nasal cavities. This nasal cycling process result in unilateral nasal airflow change over time and may cause variation in NAR measurement.

Other causes for inaccuracy include air leak, air -- nasal secretions that are common in patients with cold and rhinitis, and a pressure change from breathing or swallowing during measurement of NAR. NAR may be most useful in distinguishing mucosa from structural causes of a nasal congestion. It can also be helpful in assessing nasal anatomic abnormalities.

In terms of study design, naturally occurring cold studies and outpatient natural exposure allergic rhinitis studies should be double-blind placebo-controlled and

parallel-group studies. A placebo-controlled and double-blind study design is critical, because of the subjective nature of the primary efficacy endpoint. An active control is recommended as well.

Now, in summary, we have briefly discussed nasal congestion and its pharmacological treatment, types of clinical studies for nasal decongestions, and assessment of nasal congestion in clinical studies.

From this brief presentation, there were three take-home messages. First, patient self-assessed nasal congestion scores are the division's preferred primary efficacy endpoints, including the studies of nasal decongestants.

Second, a nasal decongestant should be tested for its efficacy in naturally occurring cold studies or in outpatient natural exposure allergic rhinitis studies. These clinical studies should be

double-blind, placebo- controlled, and parallel-group studies.

Finally, the division currently accepts nasal airway resistance as secondary or supportive efficacy endpoints in clinical studies of nasal decongestants. I'm just closing my presentation. Thank you for your attention.

DR. TINETTI: Thank you very much. We will just -- we will now open for the panel to ask clarifying questions to any members of the FDA. Again, this afternoon we will have the more general questions, so these should really be focused primarily on questions you have to clarify the presentations and address any points you don't understand.

DR. FOLLMANN: The question I had was to Dr. --

DR. TINETTI: We are asking -- if you just -- for the press, if you could identify yourself before you ask a question.

DR. FOLLMANN: Okay. I'm Dean Follmann. The question I had earlier was for Dr. Koenig and it was to point out as the -- as Dr. Lee pointed out, the W1A study that he reported as significant was significant because he compared it to baseline. When you compare the drug to placebo there is no significant effect and so the tally of 7/14 I think is more properly given as 6/14.

The other question I just have is for, I guess, the last speaker, really sort of his last comment. So he mentioned that the NAR would not be used or would not -- could not be used to show evidence of efficacy for a new drug for nasal decongestion. So it's just to clarify that if there was a new drug coming onboard over the counter for nasal decongestion, would it have to show benefit in terms of subjective symptoms or what would the bar be for a new over-the-counter drug?

MR. LEE: Hi, I am Charlie Lee. I

am clinical team leader for the Division of Pulmonary and Allergy Products. And your question, our expectation would be that the -- that that drug would need to show efficacy with the patient-assessed nasal congestion scores, whether or not if the sponsor chose to include nasal airway resistance or other measures of -- objective measures that would be certainly acceptable to us. But again, because the indication is relief of patient symptoms, we prefer the patient-assessed nasal congestion scores, because it directly addresses that.

DR. TINETTI: Did you want to respond to that question as well? Okay, go ahead. Go ahead.

MR. LIN: Not the second one, but the -- I thought I heard Dr. Follmann asking something about AHR-G1 GIA. That study -- the comparison was relative to the baseline that showed a significance -- significant reduction. But in the trial, there was no

placebo arm. So there was no placebo --

DR. TINETTI: I think his question was that included in your tally of effective studies and should it be. So I think you're saying you should take it out of the numerator and the denominator, is that what you're suggesting, Dr. --

DR. FOLLMANN: Well, maybe there is a point of confusion here, because when I read Wyeth's report of that study they -- I thought, you know, we compared it to placebo and there were no statistically significant difference among the decongestant treatments, but they did mention that it was significant compared to baseline.

DR. D'AGOSTINO: I have a couple of points and some questions.

DR. TINETTI: Please identify yourself for --

DR. D'AGOSTINO: I'm sorry, Ralph D'Agostino. I have a couple of questions, again, for clarification. When the panel was

reviewing the studies, there was a big controversy of symptoms versus objective and the field has shifted away from objective, but objective were used then. The presenters aren't telling us that we should minimize the objective and -- or are they telling us that we should minimize the objective in the studies that went into the meta-analysis, what comment are they making? I'm not sure I know what I should take away in terms of using the objective measures.

MR. LEE: I think the purpose -- again, this is Charlie Lee. The purpose is, of our presentation, was actually to focus on what would be -- what we would need to see or what we would expect, if further studies are necessary. We clearly did not assess the efficacy, the manner of efficacy, the assessment in the studies that the panel reviewed that was not what we were asked to do. And clearly, one gets into a situation that -- it's difficult to look at analyses

and discussion that occurred 20 or 30 years ago through the microscope today.

So we totally wanted to stay away from that. And again, our purpose was to focus on what would be required if we needed to have clinical studies in the future.

DR. D'AGOSTINO: Okay. And my second question -- thank you for that. My second question is we are spending a lot of time on meta-analysis. I'm not sure that meta-analysis is necessarily for approval of effectiveness as opposed to looking at each individual study and talking about the quality of the study. Are the speakers from the FDA implying because they've spent all their time talking about the meta-analysis that somehow or the other the meta-analysis becomes the way we should judge effectiveness as opposed to looking at each individual study and carrying away the message of the studies?

DR. JOHNSON: Hi, this is Susan

Johnson. I'd like to address both of the questions that you posed. I think there is a difference in view point potentially from the NDA versus the monograph side. The one thing that we didn't want to do at this committee is revisit the decision that the panel made at the time that it made it.

There is not a clear reason to review just those studies and look at how they specifically made their decision in a vacuum, because we can't replicate that scenario. So in looking at whether or not the balance has shifted from objective to subjective scores, that's something that we need the panel's help with is to understand how we want to move, if we do, towards a different set of assessments. The only way that we could explain any sort of tangible shift is to look at what was required for the NDAs right now. How that reflects on the monograph is really the basis of the discussion today.

And the second point is, under an NDA, and now currently under a monograph, no meta-analysis would be required. The reason that the meta-analysis is figuring prominently into the discussion is because that's how the petitioner raised the question. And so that's really the basis for including that in the discussion and I think the meta-analysis from the petitioner generated the meta- analysis to some extent from CHPA.

DR. D'AGOSTINO: So in our evaluation, if you want to make a comment about effectiveness, we do well to look at the individual studies and the quality of the individual studies; we obviously are going to make comments on the meta-analysis too?

DR. JOHNSON: That's certainly a valid way to look at it and if that's something that the panel finds the more relevant way to look at it, that's something that we would like to hear about.

DR. D'AGOSTINO: Thank you.

DR. NELSON: Ed Nelson. I have two questions for the FDA, I guess, Dr. Wang I was thinking would maybe answer it or whoever. And one of them has to do with making efficacy and comparative claims based on the allergen exposure chamber studies. Is that something you would allow now or accept? And I just wanted to confirm what you said that the chamber study is not accepted now as a pivotal study, is that -- what I'd call one of the two pivotal studies. Is that correct?

MR. LEE: Okay, yeah, okay, it works. The -- we find the chamber studies are -- would not be sufficient to support as a pivotal study approvable drug for treatment of nasal congestion. However, it may -- they do provide information. And again, we see it as being a sensitive pharmacodynamic measure, very controlled, and actually, quite useful in establishing things like onset of action, duration of action, that type of thing.

DR. NELSON: But would you allow it then to be used to as a -- in comparative claims, the chamber studies?

MR. LEE: In comparative claims, it would depend upon what that claim would be. I mean, again, it was an onset of action claim and that particular claim was supported in replicate and -- well, with the chamber study and was not shorter than the natural study. It could do that, but it would be specifically for something like a claim of onset of action.

DR. TINETTI: Mr. Fitzgerald?

DR. FITZGERALD: That's right. Garrett FitzGerald. I'd just like to come to the blood pressure question and ask for clarity as to whether there's ever been a study that has been designed appropriately to address the blood pressure question at either 10 or 25 milligrams. And by that I mean, powered appropriately to detect what might be a reasonable change, 3 to 4 millimeters with

measurements such as continuous measurement of blood pressure that might be appropriately sensitive and controlling for factors that might modulate drug response, such as the time of day which is known to modulate the blood pressure response to phenylephrine in humans.

DR. TINETTI: I expect by the way you worded the question you know the answer, but does anybody want to take that one up?

DR. KOENIG: This is Michael Koenig, or "Kaynig."

(Laughter)

DR. KOENIG: My dad says "Kaynig" and his dad said Koenig, so I got to pick I guess. The data that we have on safety and in particular on safety, but even the data that we have on effectiveness for most of the studies that we looked at, is very limited. It comes in the form of summary memoranda, and typically what we see is very -- is a page or two describing what they found for

effectiveness and then a paragraph maybe that says, well, blood pressure was fine. So there were no details, or there were certainly insufficient details to address that.

I'm not aware of any specific studies that went into that kind of detail of those that we looked at.

DR. HONSINGER: I have two questions and a comment, if I may.

DR. TINETTI: Just identify yourself.

DR. HONSINGER: Richard Honsinger. First question is, were there any studies that looked at doses higher than 25 milligrams, that is, is there -- will we be meeting again in a year or two, looking at 50 or 100?

DR. KOENIG: Michael Koenig again. There were doses that looked at higher -- up to 75 milligrams was the highest dose that was evaluated. What we saw was essentially a

number of dose ranging studies that basically centered around 10 to 25, but there was one study that looked at 75 and 50, and that same study evaluated 50 milligrams. In those studies neither of -- and that study, which actually was that first study that I mentioned that had healthy -- apparently healthy non- congested individuals, they didn't find an effect, but --

DR. TINETTI: So are you saying there have been no studies in people that were symptomatic at doses higher than 25? Was the only higher dose on -- in a healthy population?

DR. KOENIG: I'm saying that of the studies we looked at, there were none, right.

DR. HONSINGER: Another question. I'm in practice and my patients have gotten older and particularly my men are worried about urinary obstruction. We are treating with -- we are dealing with a drug that's an alpha-adrenergic blocker. I didn't see any

mention of adverse events looking at urinary obstruction. Were those mentioned in any of the papers or did they study that appropriate population?

DR. KOENIG: Phenylephrine is an alpha 1 selective agonist, and no, that wasn't mentioned in any of the papers. Only the cardiovascular risks were addressed. Yes, sir.

DR. HONSINGER: Richard Honsinger, I have more comment. Last weekend I was cleaning out my closet looking for Christmas decorations and I found my rhinomanometer.

(Laughter)

DR. TINETTI: Did you bring it with you?

DR. HONSINGER: It was kind of dusty and I quit using it about 20 years ago, because the difficulty in measuring rhinomanometry. You have to understand that this -- although it's an objective measurement, the nose is an erectile organ.

(Laughter)

DR. HONSINGER: And it varies. I mean, Dr. Wolfe wrote a book in the 1950s or '60s on the nose in psychiatry and how the nose reflects psychiatric moods, and that's certainly true when you try to measure rhinomanometry. Patient's nose is just sometimes stuffy, sometimes they are open and it isn't the drug effect, so your baseline is tremendously variable.

In addition, it's very difficult to measure. We finally had to go and make a -- and go to the dentist and make casts of people's noses and make a paraffin adaptor that would fit everybody's nose. They did good rhinomanometry back in the 1980s, so it's a difficult technique that has a tremendous amount of variability without drugs.

DR. TINETTI: Thank you for that insight. Dr. Ownby?

MR. OWNBY:: Dennis Ownby. I had a

question or clarification for Dr. Koenig or Koenig, whichever he prefers at the moment. I take it from your summary of all these studies that there are not numbers sufficient to allow any estimation of whether there are selectively different populations within this, that is, older versus younger adults, males versus females or different racial or ethnic groups, and the way they might respond?

DR. KOENIG: And your assumption is correct. There is not sufficient data. Typically for demographics, if we get anything it was the age, and there was some mention of male versus female, but no analysis in terms of male versus female or older versus younger responses.

SPEAKER: Not typical.

DR. KOENIG: It wasn't typical.

DR. TINETTI: I have a related question to that. Of the studies that we've heard, and recognizing that the standards

were different at that time, do any of the studies we hear about today meet criteria if this was coming through as a new drug? I mean, do any of the studies that we have in front of us meet the present standards and criteria, and if so, which ones?

MR. LEE: -- look at the -- those studies in detail and that's not what we were asked to do. That said, if we are looking at studies with our preferred primary efficacy endpoint, it would be -- we would expect to see studies that are larger in size. And so I think in some respects the -- I mean, again, as far as the designs of the studies as well, I mean, when you look at the reports as you have, they really -- we'd have to say, they really would not meet the standards of what we would expect as far as study report, the kind of information. I'm not sure, is that the type of --

DR. TINETTI: Right, so what you're saying is none of these studies that we are

hearing about today -- are talking about today would meet present standards?

MR. LEE: Yeah, from -- I can't say from a quick read that would be true.

DR. TINETTI: Okay, thank you.

DR. JOHNSON: Could I just add that I think we didn't, as Dr. Lee said, evaluate these under NDA criteria. The newer studies may -- where they submitted under an NDAB considered support of as EEU studies and were intended to be conducted in that mode, so --

DR. TINETTI: We understand. Thank you. Dr. Shrank.

DR. SHRANK: I'm Will Shrank. I'm trying to just get a better sense of where the nasal airway resistance studies fit into the picture. So have there been validation studies to give us a sense of how well the nasal airway resistance tracks with subjective symptoms, maybe for Dr. Wang?

MR. LEE: No, they're not. If one can actually get -- I mean, one can actually

look at the results that -- from the studies here and then there is -- I mean, I think we can say from what's on the table there is a general rough correlation, there is a concordance with a big eye looking at it. And where there is concordance, the concordances more on the side of efficacy than not, so again, it's about all that I can say about the studies that are here.

DR. KOENIG: Michael Koenig. It's -- there are a number of published comparisons of subjective and objective efficacy endpoints. And there have been some suggestions, particularly by the gentlemen I mentioned, Eccles and Schumacher who are proponents of NAR that suggest that there are conditions under which the two correlate better.

Typically, that's a longer experiment. It's a case where technicians are fully trained and there is some sort of standardization in the -- in terms of the use