FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEETING

(NDAC)

Virtual Meeting

Day 1

Monday, September 11, 2023

9:00 a.m. to 4:51 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Jessica Seo, PharmD, MPH

Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Kristy Brittain, PharmD, BCPS, CDCES

Professor, Medical University of South Carolina
College of Pharmacy
Clinical Pharmacy Specialist, MUSC Health
Charleston, South Carolina

Stephen C. Clement, MD

Associate Professor of Medical Education
University of Virginia School of Medicine
Practicing Physician, INOVA Fairfax Hospital
Falls Church, Virginia

Diane B. Ginsburg, PhD, MS, RPh, FASHP
Clinical Professor, Pharmacy Practice Division
Associate Dean for Healthcare Partnerships
The University of Texas at Austin
College of Pharmacy
Austin, Texas

Tonya S. King, PhD
Professor of Biostatistics
Department of Public Health Sciences,
The Pennsylvania State University College of Medicine
Hershey, Pennsylvania

Paul Pisarik, MD, MPH, FAAFP
Geriatric Physician
Archwell Health
Tulsa, Oklahoma

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Mark E. Dato, MD, PhD

(Industry Representative)

Retired: Director, Global Technology, Procter and Gamble Healthcare

Evanston, Illinois

TEMPORARY MEMBERS (Voting)

Maryann Amirshahi, PharmD, MD, MPH, PhD

Professor of Emergency Medicine

Georgetown University School of Medicine

Department of Emergency Medicine

MedStar Washington Hospital Center

Associate Medical Director

National Capital Poison Center

Washington, District of Columbia

Susan J. Blalock, PhD
Professor Emeritus
Eshelman School of Pharmacy
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

TEMPORARY MEMBERS (Voting) (cont.)

Karim Anton Calis, PharmD, MPH, FASHP, FCCP
Senior Scientist
Director of Clinical Research and Compliance
Office of the Clinical Director
Division of Intramural Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Chair, Institutional Review Board
Office of Intramural Research
National Institutes of Health
Hatfield Clinical Research Center
Bethesda, Maryland

Maria C. Coyle, PharmD, FCCP, BCPS, BCACP, CLS

(Acting Chairperson)

Associate Professor – Clinical

Specialty Practice Pharmacist

The Ohio State University

Columbus, Ohio

Emma H. D'Agostino, PhD

(Acting Consumer Representative)

Consultant

Cystic Fibrosis Foundation

Lead Medical Writer, BOLDSCIENCE

Atlanta, Georgia

Mark Dykewicz, MD

Raymond and Alberta Slavin Endowed Professor

in Allergy and Immunology

Saint Louis University School of Medicine

Saint Louis, Missouri

William D. Figg, PharmD, MBA
Senior Investigator
Associate Director, Center for Cancer Research
Acting Chief, Genitourinary Malignancies Branch
Chief, Clinical Pharmacology Program
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

Bridgette Jones, MD, MS
Professor of Pediatrics,
Divisions of Allergy/Asthma/Immunology and Pediatric Clinical Pharmacology, Toxicology, and Therapeutic Innovation,
Children's Mercy Hospitals and Clinics
Kansas City, Missouri

Esther Kim, MD, FARS

Assistant Professor, Otolaryngology/Head Neck Surgery

Uniformed Services University of the Health Sciences

Chief, Otolaryngology/Head Neck Department

Fort Belvoir, Virginia

Jennifer Le, PharmD, MAS, FIDSA, FCCP, FCSHP

Professor of Clinical Pharmacy

University of California San Diego

Skaggs School of Pharmacy and Pharmaceutical Sciences

La Jolla, California

Jennifer A. Schwartzott, MS

(Patient Representative)

North Tonawanda, New York

FDA PARTICIPANTS (Non-Voting)

Theresa Michele, MD
Director
Office of Nonprescription Drugs (ONPD)
Office of New Drugs (OND), CDER, FDA

Nushin Todd, MD, PhD
Director
Division of Nonprescription Drugs I (DNPD I)
ONPD, OND, CDER, FDA

Martha Lenhart, MD, PhD
Deputy Director
DNPD I, ONPD, OND, CDER, FDA

Steven Adah, PhD
Associate Director for Monographs
DNPD I, ONPD, OND, CDER, FDA

Peter Starke, MD
Lead Clinical Reviewer
DNPD I, ONPD, OND, CDER, FDA

Ben Bishop, PharmD, MSc Reg Sci

Regulatory Review Officer

DNPD I, ONPD, OND, CDER, FDA

Yunzhao Ren, MD, PhD

Team Leader

Division of Inflammation & Immune Pharmacology (DIIP)

Office of Clinical Pharmacology (OCP)

Office of Translational Sciences (OTS)

CDER, FDA

Tracy Pham, PharmD

Drug Utilization Analyst

Division of Epidemiology II (DEPI II)

Office of Surveillance and Epidemiology (OSE)

CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. COYLE: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Cherie Duvall-Jones. Her e-mail is currently displayed.

My name is Dr. Maria Coyle, and I will be chairing this meeting. I will now call Day 1 of the September 11th and 12th 2023 Nonprescription Drugs Advisory Committee meeting to order. Dr. Jessica Seo is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. SEO: Thank you, Dr. Coyle.

Good morning. My name is Jessica Seo, and I am the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll begin with the standing members of the NDAC,

and start with Dr. Kristy Brittain.

DR. BRITTAIN: Good morning. Kristy Brittain. I'm from the Medical University of South Carolina, a professor, and I am a clinical pharmacy specialist with MUSC Health.

DR. SEO: Thank you, Dr. Brittain.

Next, we have Dr. Clement.

DR. CLEMENT: Good morning to all of you. Stephen Clement. I am a practicing endocrinologist at Inova Health System in Northern Virginia and have expertise in endocrine diseases. So the content of this committee for this topic is going to be very interesting to me because this is a lot of new information.

DR. SEO: Thank you.

Next is Dr. Ginsburg.

DR. GINSBURG: Good morning. I'm Diane Ginsburg. I'm a clinical professor of pharmacy practice and the associate dean for Healthcare Partnerships in the College of Pharmacy at the University of Texas at Austin.

DR. SEO: Thank you.

Dr. King?

DR. KING: Hi. I'm Tonya King. I am professor of biostatistics at Penn State College of Medicine.

DR. SEO: Thank you.

And Dr. Pisarik?

DR. PISARIK: Paul Pisarik, family medicine, epidemiology. I work for Archwell Health in Tulsa, Oklahoma.

DR. SEO: Thank you.

Next, we have our non-voting industry representative to the NDAC, Dr. Dato.

DR. DATO: Mark Dato, industry rep for the Nonprescription Drug Advisory Committee and pediatric pulmonary retired.

DR. SEO: Thank you.

We'll now introduce our temporary voting members, and begin with Dr. Amirshahi.

DR. AMIRSHAHI: Good morning. Maryann Amirshahi. I am an emergency medicine physician. I'm professor of emergency medicine at Georgetown University School of Medicine and a medical

toxicologist at the National Capital Poison Center, as well as a clinical pharmacologist. Thank you.

DR. SEO: Thank you.

Next, we have Dr. Blalock.

DR. BLALOCK: Hi. I'm Sue Blalock. I'm a professor emeritus at the School of Pharmacy at the University of North Carolina Chapel Hill, and my area of expertise is medication risk communication.

DR. SEO: Thank you.

And we have Dr. Calis.

DR. CALIS: Good morning. My name is Karim Calis. I'm a senior scientist at the NIH in Bethesda, Maryland, currently working as director of Clinical Research and Compliance for the National Institute of Child Health and Human Development, and also chair of the NIH IRB. Thank you.

DR. SEO: Next is Dr. Coyle.

DR. COYLE: Good morning again. I'm Maria Coyle. I'm an associate professor at the Ohio State University College of Pharmacy and a ambulatory care pharmacy specialist at our Wexner

Medical Center.

DR. SEO: Thank you.

Next is Dr. D'Agostino.

DR. D'AGOSTINO: Good morning. I'm Emma D'Agostino. I'm a consumer representative. I am an advocate with the Cystic Fibrosis Foundation and a biochemist by training.

DR. SEO: Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: Hi. I'm Mark Dykewicz. I'm an allergist-immunologist, chief of allergy and immunology and professor of internal medicine at Saint Louis University School of Medicine in Saint Louis.

DR. SEO: Thank you.

Next is Dr. Figg.

DR. FIGG: Hi. William Figg. I'm an investigator at the National Institutes of Health, clinical pharmacologist, also associate director of the Center for Cancer Research in the National Cancer Institute.

DR. SEO: Thank you.

Dr. Jones?

DR. JONES: Good morning. My name is Dr. Bridgette Jones. I am a professor of pediatrics at University of Missouri, Kansas City School of Medicine. I'm also a pediatric allergist and pediatric clinical pharmacologist at Children's Mercy Hospital in Kansas City.

DR. SEO: Thank you.

We also have Dr. Kim.

DR. KIM: Good morning. My name is Esther Kim. I'm an active duty physician stationed at Fort Belvoir. I'm an associate professor of surgery at the Uniform Services of Health Sciences, and I'm an otolaryngologist and rhinologist.

DR. SEO: Thank you.

Next is Dr. Jennifer Le.

DR. LE: Good morning. I'm Jennifer Le, professor of clinical pharmacy at the Skaggs School of Pharmacy at the University of California San Diego. I'm a pediatric and infectious disease specialist.

DR. SEO: Thank you, Dr. Le.

And Ms. Jennifer Schwartzott?

MS. SCHWARTZOTT: Hello. I'm Jennifer Schwartzott, and I'm your patient representative.

DR. SEO: Thank you.

We'll now go to our FDA participants, and begin with Dr. Michele.

DR. MICHELE: Good morning, everyone. My name is Dr. Theresa Michele. I'm the director of the Office of Nonprescription Drugs in CDER, and I am a practicing pulmonary critical care specialist.

DR. SEO: Thank you.

Next, we have Dr. Todd.

DR. TODD: Good morning, and welcome. I'm Nushin Todd. I'm the director of the Division of Nonprescription Drugs I in the Office of Nonprescription Drugs, and my training is in medical oncology. Thank you.

DR. SEO: Thank you.

And we have Dr. Lenhart.

DR. LENHART: Good morning. My name is Martha Lenhart. I am the deputy director for the Division of Nonprescription Drugs I in the Office

of Nonprescription Drugs. Thank you.

DR. SEO: Thank you.

And next we have Dr. Adah.

DR. ADAH: Good morning. My name is Steven Adah. I'm the associate director for monographs in the Division of Nonprescription Drugs I. Thank you.

DR. SEO: Thank you.

Dr. Starke?

DR. STARKE: Good morning. I'm Dr. Peter Starke. I'm the lead clinical reviewer, and I'm in the Division of Nonprescription Drugs I.

DR. SEO: Thank you.

Next is Dr. Bishop.

LCDR BISHOP: Good morning. My name is Ben Bishop, and I'm a reviewer in the Office of Nonprescription Drugs.

DR. SEO: Thank you.

We also have Dr. Ren.

DR. REN: Good morning, everyone. My name is Yunzhao Ren, the acting team leader of the Division of Inflammation and Immune Pharmacology in

the Office of Clinical Pharmacology, in FDA. Thank you.

DR. SEO: Thank you.

And finally, Dr. Pham.

DR. PHAM: Good morning. My name is Tracy Pham. I'm a drug use analyst from the Division of Epidemiology, the Office of Surveillance and Epidemiology.

DR. SEO: Thank you all, and I'll return the floor to Dr. Coyle.

DR. COYLE: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this 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 chairperson. 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 this 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, and also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Seo will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Coyle.

The Food and Drug Administration, or FDA, is convening today's meeting of the Nonprescription Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, or FACA, of 1972. With the exception of the industry representative, 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 this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee 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 and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government

may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children and, for 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 new data regarding the Generally Recognized as Safe and Effective, or GRASE, status of oral phenylephrine as a nasal decongestant that have become available since FDA last examined the issue. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by committee members and temporary voting members, no conflict

of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Mark Dato is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Dato's role at this meeting is to represent industry in general and not any particular company. Dr. Dato is retired.

We would like to remind members and temporary voting members that if the discussions involve any other topics 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 regarding the topic that could be affected by the committee's discussions.

Thank you, and I'll return the floor to you, Dr. Coyle.

DR. COYLE: Thank you.

We will now proceed with FDA introductory remarks from Dr. Theresa Michele, followed by Lieutenant Commander Bishop.

Introduction and Regulatory History

Theresa Michele

DR. MICHELE: [Inaudible - audio gap] -- of the Office of Nonprescription Drugs. On behalf of FDA and the office, it is my pleasure to welcome you to the meeting of the Nonprescription Drugs Advisory Committee, where we will be discussing the efficacy of oral phenylephrine as a nasal decongestant.

Now, I especially want to thank our advisory committee members who are offering up their time and expertise today, as well as members of the Consumer Healthcare Products Association, who have

graciously agreed to represent industry. In addition, I want to thank the academicians and the members of the public who will be stepping forward at the open public hearing to present their views.

So as I alluded to already, the main objective of today's meeting is to discuss the efficacy of oral phenylephrine as a nasal decongestant. We will be including data that have become available since the committee last discussed this back in 2007. We're also asking you to consider the potential safety and efficacy of higher than monographed doses of oral phenylephrine.

Now, as you all know, phenylephrine is a very old drug. It's been marketed for more than 75 years for a variety of uses and via a variety of different routes of administration. Anytime a product's been on the market for that long, it's human nature to make assumptions about what we think we know about the product. For the purposes of today's meeting, we're asking you to put aside those assumptions and help us think critically

about the data at hand; and in particular, what the data may or may not show.

Phenylephrine is one of two orally administered alpha-1 adrenergic receptor agonists that are generally recognized as safe and effective, or GRASE, in the cough-cold monograph. This indication is for temporary relief of nasal congestion, and it's regardless of the underlying etiology.

Phenylephrine is also GRASE in the OTC drug monograph for direct intranasal use to treat congestion; for topical use to treat hemorrhoids; and for ocular use to treat redness of the eye. On the prescription side, phenylephrine is approved in a variety of formulations, including intravenous for treatment of hypotension due to vasodilation and ocular to dilate the pupil. This meeting focuses entirely on the use of oral phenylephrine for the treatment of nasal congestion.

This slide is a listing of all of the ingredients in the cough-cold monograph, which, as you can see, encompasses a variety of different

active ingredient classes, ingredients, and routes of administration. Again, today we're focusing on the oral decongestants that are shown in the black box, and specifically on phenylephrine, which is shown in red font. There are two different phenylephrine salts: phenylephrine hydrochloride and phenylephrine bitartrate. The bitartrate salt was added to the monograph in 2006 based on PK matching to the hydrochloride salt. Although phenylephrine is also listed as a topical decongestant, we are not considering that use today.

This slide shows the oral doses for both salts. Highlighted is the monographed adult and adolescent dose of the hydrochloride salt, which is the basis of the GRASE finding, and it was the dose that was used in almost all of the clinical trials and studies. The dosage is 10 milligrams every 4 hours, not to exceed 60 milligrams in 24 hours.

Now, since efficacy of the bitartrate salt is extrapolated from that of the hydrochloride salt, we will not be discussing the bitartrate salt

directly. Likewise, efficacy of phenylephrine in children was extrapolated from adults, and so we will not be directly discussing pediatric efficacy. Because of the extrapolation, however, we anticipate that any recommendations of the advisory committee with regard to efficacy of oral phenylephrine in adults may be also applicable to children and to the bitartrate salt.

So, because science continues to discover new things and drug development continues to evolve, it's not uncommon that we learn additional information about drugs that have been on the market for some time, and phenylephrine is no exception.

Some of the additional data was brought forward in two citizen petitions, one in 2007 and one in 2015. The 2007 citizen petition requested that the agency amend the dosages of both oral phenylephrine salts by increasing the maximum allowed dosage for patients 12 years of age and older. It also requested that FDA withdraw approval, or rather make it not GRASE, for use in

children less than 12 years of age. The 2015 citizen petition requested that FDA reclassify the oral phenylephrine salts as not GRASE due to lack of efficacy.

So, because of the additional data that had become available since FDA's GRASE finding back in 1994, we convened an advisory committee in 2007 to discuss the safety and effectiveness of oral phenylephrine as a nasal decongestant. At the meeting in 2007, the committee also considered the original study supporting the effectiveness of oral phenylephrine.

The committee noted that the results are not consistent across studies for nasal airway resistance and recommended that symptoms should be the essential primary endpoint. They also noted that evidence of efficacy consisted primarily of studies conducted 40 years ago, which is now 55 years ago, and it included fewer than 200 subjects who received oral phenylephrine 10 milligrams.

Due to the small size of the studies, they

felt that nasal airway resistance results may not be generalizable to a wider population. Based on this, the committee recommended that additional data be conducted, specifically multicenter, parallel, randomized, double-blind, placebo-controlled trials, preferably with an active control such as pseudoephedrine to evaluate nasal congestion scores and symptom relief.

They also recommended characterization of the phenylephrine dose response and dosing interval, comparison of the PK of single-ingredient products versus multiple-ingredient products, and a safety evaluation of the effects of phenylephrine on blood pressure. I'm pleased to say that we now have much of the data that was requested by the 2007 advisory committee, and we are now bringing this back to this committee for consideration.

So as you consider the data that are brought before you today, it may be helpful to put it into context of the regulatory standard for effectiveness under the monograph, which is spelled out in 21 CFR 330.10. This standard states that

effectiveness means a reasonable expectation that in a significant portion of the target population, the pharmacological effect of the drug will provide clinically significant relief of the type claimed. It goes on to state that proof of effectiveness shall consist of controlled clinical investigations as defined in 21 CFR 314.126(b).

So what is that? Well, that reg links back to the definition of adequate and well-controlled studies for a new drug application, which of course you're all familiar with. One of the differences for you to consider with the monograph compared to NDAs in terms of the standards is because monographed drugs are generally recognized as safe and effective.

That means that the data must be publicly available for the public to comment on prior to FDA making a final determination. In addition, under the monograph, rather than talking about a single drug product, the evaluation pertains to all drug products that fulfill the conditions of use of the monograph.

Finally, I'll conclude with the purpose of proceedings before an advisory committee, which is also spelled out in regulation. Specifically, an advisory committee is utilized to conduct public hearings on matters of importance that come before FDA to review the issues involved and to provide advice and recommendations to the commissioner. The commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee.

Now, as such, we are not asking you to make a GRASE determination today on phenylephrine as an oral decongestant; rather, we are asking you to advise us on what you believe the data show in terms of effectiveness. Again, we greatly appreciate your input on this important topic, and we look forward to thoughtful scientific dialogue. Thank you. I'll hand it over to Dr. Ben Bishop, who will be presenting on the regulatory history of phenylephrine. Thank you.

Introduction and Regulatory History

Ben Bishop

LCDR BISHOP: Good morning. My name is Ben Bishop. I am a pharmacist, and since joining FDA in 2010, I've spent a great deal of time working with OTC monograph ingredients generally. I've also completed numerous assignments working with the nasal decongestant category, and phenylephrine specifically. The purpose of my presentation today is to provide background and important context for the regulatory history of oral phenylephrine.

Although the agency first took regulatory action in 1976, this action was based on the conclusions and recommendations of an advisory review panel, which was convened in November of 1972. Not to be confused with other types of panels or advisory committees, that panel and others like it are known as DESI review panels. DESI stands for Drug Efficacy Study Implementation, and the DESI panels represented one of the agency's pivotal first steps in a long process of rulemaking. Almost 20 years later, the final monograph for nasal decongestants, part of the larger Colds, Cough, Allergy, Bronchodilator, and

Antiasthmatic monograph, was published in 1994.

I will ascribe the agency publications issued throughout this process, as well as additional events on this timeline later on in my presentation, but first the impacts of the DESI panel's review on the inclusion of oral phenylephrine in the monograph merits a closer look.

In 1962, a retrospective evaluation of drug efficacy was authorized by the Kefauver-Harris Amendment. Notably, the law mandated that FDA evaluate effectiveness, whereas previous approvals have required only a determination of safety. For nonprescription drugs, the Drug Efficacy Study Implementation, or DESI review, began 10 years later when FDA assembled a list of over 400 active ingredients being marketed without a prescription and categorized them into 26 therapeutic categories. One of these became known as the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic monograph, or CCABA monograph, and this included nasal decongestants.

The DESI panel was charged with making recommendations based on their best scientific judgments and the available data to establish conditions of use with respect to dosing, directions, and warnings. At that time, a definition for OTC drug effectiveness standard was established in 21 CFR 330.10, as Dr. Michele described; then the DESI panel was charged with applying this standard, 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 DESI panel report published in 1976 defined nasal decongestants as agents that reduce nasal congestion in patients with acute or chronic rhinitis. They evaluated phenylephrine hydrochloride and pseudoephedrine as oral nasal decongestants, and concluded that phenylephrine hydrochloride is safe and effective as an orally

administered nasal decongestant for OTC use at the specified dosage.

With this information, FDA was responsible for creating and implementing the regulations which govern the OTC monograph. After considering the DESI panel's recommendations, the agency applied the three-step rulemaking process used at the time, sometimes referred to as "Notice and Comment."

In step 1, the 1976 Advance Notice of Proposed Rulemaking announced the agency's proposal to include phenylephrine in the OTC monograph based on the panel's recommendation. The agency decided to issue the unaltered conclusions and recommendations of the panel, and stated that the purpose of this approach was to, quote, "stimulate discussion, evaluation, and comment on the full sweep of the panel's deliberations."

In step 2, the 1985 tentative final monograph, or proposed rule, included the agency's evaluation of all available data and comments received after the ANPR. At that time, the agency maintained its position that phenylephrine be

included in the monograph. At this stage, the numbered categories -- category 1 representing generally recognized as safe and effective; category 2 representing not generally recognized as safe and effective; and category 3 representing insufficient data available and further testing required -- were used to classify each active ingredient relative to its therapeutic claim in the proposed rule. Topical and oral phenylephrine were proposed as category 1 or GRASE. In step 3, the 1994 final monograph, or final rule, established the agency's classification of oral and topical phenylephrine hydrochloride as monograph conditions.

Phenylephrine bitartrate is an effervescent tablet dosage form formed with the bitartrate salt. FDA received a citizen petition in 2002, which requested that the CCABA OTC monograph be amended to add this dosage form of phenylephrine. The petition did not include efficacy data. It was, however, submitted with domestic and global marketing history data, and pharmacokinetic data

showing that phenylephrine hydrochloride and phenylephrine bitartrate have comparable bioavailability profiles. FDA issued a proposed rule in 2004, and then a final rule in 2006, to add phenylephrine bitartrate as a monograph condition. Again, we note that this determination was based on pharmacokinetic matching data, not efficacy.

I will briefly describe two other active ingredients, as they are relevant to phenylephrine's use as an oral nasal decongestant. Pseudoephedrine is the only other oral decongestant listed in the CCABA monograph. The Combat Methamphetamine Epidemic Act was enacted in 2006, restricting public access to pseudoephedrine. The act required that pseudoephedrine be sold behind the counter and also limited purchase quantities. This led to many products being reformulated to contain phenylephrine instead of pseudoephedrine and dramatically affected the OTC nasal decongestant market. These effects will be discussed later.

Phenylpropanolamine was recommended as safe

and effective by the panel in 1976, however, by 1985, FDA had received numerous comments and data related to phenylpropanolamine's use both as a nasal decongestant as well as a weight control drug. It was not found GRASE as a nasal decongestant, and was later removed from the weight control monograph after additional safety data demonstrated an association with hemorrhagic stroke in women of childbearing age.

In 2020, the Coronavirus Aid Relief and Economic Security, or CARES Act, modernized the way that OTC monographed drugs are regulated in the United States. The burdensome rulemaking process was often characterized by delays, whereas the administrative order process is expected to improve efficiency and facilitate innovation. All OTC monographs have now been reviewed and posted as orders. Specifically, the CCABA OTC final monograph was posted on October 14, 2022.

This concludes my presentation. I hope I've been able to adequately review and clarify phenylephrine's long regulatory history. Thank

you.

DR. COYLE: Thank you.

We will go ahead and take a short 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during this break. We will resume at 9:45; 9:45 we'll see everyone back here. Thank you.

(Whereupon, at 9:36 a.m., a recess was taken, and meeting resumed at 9:45 a.m.)

DR. COYLE: Welcome back. We will now proceed with FDA's presentation, starting with Dr. Yunzhao Ren.

FDA Presentation - Yunzhao Ren

DR. REN: My name is Yunzhao Ren, the clinical pharmacology acting team leader from the Division of Inflammation and Immune Pharmacology, Office of Clinical Pharmacology from FDA. I have been reviewing the phenylephrine products since 2014, the clinical pharmacological part, in FDA. My slides today will briefly cover the clinical pharmacology aspect of phenylephrine.

The role of the clinical pharmacology presentation in this meeting is to provide a mechanistic explanation to the lack of nasal decongestive effect following the monographed oral dose of phenylephrine that was observed from recently conducted randomized, placebo-controlled clinical efficacy trials with a relatively large sample size.

I'll first introduce the metabolism and pharmacology of phenylephrine, then I will explain in detail why phenylephrine has very low bioavailability via the oral administration route when compared to IV administration routes, and this low oral bioavailability of phenylephrine only results in small and transient systemic alpha-1 adrenergic activity observed from clinical trials.

Of note, because only phenylephrine hydrochloride drug products were used in the clinical PK trials, whenever I cite phenylephrine products in my presentation, I mean phenylephrine hydrochloride drug products.

Following the oral administration, more than

80 percent of the phenylephrine dose is absorbed into the human body, however, mostly in the form of metabolites. That's because extensive metabolism occurs when phenylephrine passes through the intestinal wall during the absorption. Glucuronide-conjugated phenylephrine, sulfate-conjugated phenylephrine, and hydroxymandelic acid are the three major metabolites detected in the systemic circulation and account for approximately 90 percent of the systemic exposure and urine excretion of the phenylephrine-related molecule. Meanwhile, the parent phenylephrine only accounts for about 3 percent of the total urine excretion of phenylephrine-related molecules after oral administration.

When phenylephrine is applied locally via intranasal administration route, its nasal decongestive effect is attributed to its direct alpha-1 adrenergic agonistic pharmacology effect, which constricts the blood vessels in the nasal mucosa that reduces local edema and perfusion.

Schering-Plough compared the in vitro alpha-1 adrenergic pharmacology results of phenylephrine and its major metabolites in a 2007 Nonprescription Drug Advisory Committee meeting. The results confirmed the selectivity of phenylephrine as an alpha-1 adrenergic agonist, as the EC_{50} values for alpha-1 receptors are lower than alpha-2 receptors. In addition, the in vitro results demonstrated that three major phenylephrine metabolites identified in the human body did not have any adrenergic agonistic activity at the highest tested concentration, which is consistent with the approved phenylephrine drug label that says the metabolites are considered not pharmacologically active.

In the same 2007 AC meeting, Schering-Plough also compared parent phenylephrine PK profile with the total phenylephrine PK profile following the monographed 10-milligram oral dose. The total phenylephrine, which is a coined term in this field, included both parent phenylephrine and phenylephrine that was hydrolyzed from major

conjugated metabolites during the sample preparation, and that's due to the convenience of the bioanalytical assay. I'll explain this more later.

The results show that the parent phenylephrine systemic exposure is less than 1 percent of the total phenylephrine systemic exposure. And since the amount of the total phenylephrine systemic exposure is less than the phenylephrine oral dose, the oral bioavailability of parent phenylephrine is concluded to be less than 1 percent of the oral dose. We acknowledge this is inference, but this inference is airtight.

Let me explain a little bit more about the bioanalytical assay for this total phenylephrine measurement since CHPA raised this question during their presentation later. Here, the concept of that is, if you compare the exposure, especially the AUC value, from 1 molecule to the other, a fair comparison will be compare the molar ratio, not the exact nanogram per mL or the concentrations in this unit. So therefore, I will describe here how this

black curve, the total phenylephrine, is measured.

Here what I'm measuring is generally the phenylephrine itself, including parent phenylephrine, which is just a teeny-tiny component, and also the phenylephrine that was hydrolyzed from the metabolites, especially the conjugated metabolites during the sample preparation, because for measuring the total phenylephrine, you need to incubate the samples with acid to hydrolyze the metabolites to release the phenylephrine. So here 1 molar of conjugated metabolite will give you 1 molar of phenylephrine; so it's tight, a 1-to-1 ratio, even in the molar ratio.

More importantly, the mean maximum plasma concentration, or C_{max} value of phenylephrine, is about 0.65 nanogram per mL following the monographed 10-milligram oral dose, which is lower than that in vitro alpha-1 adrenergic agonistic EC_{50} value, as shown in the next slide.

Here, you may appreciate the in vitro phenylephrine EC_{50} values are 16.9 nanogram per mL

and 2.3 nanogram per mL for alpha-1a and alpha-1b receptors, respectively. These EC_{50} values are within the range of literature reported values; however, the in vivo phenylephrine mean C_{max} value is only about 0.65 nanogram per mL following the 10-milligram oral dose in Schering-Plough's PK study. Of note, the result of low bioavailability of phenylephrine following the oral administration route was not available at the time of the original GRASE status determination for oral phenylephrine about 30 years ago.

The Schering-Plough's PK comparison results were independently confirmed by the clinical pharmacology review of NDA 022565, which was approved in 2010, and the 505(b)(2) path rely on the efficacy and safety of the oral phenylephrine monograph. The PK profiles of parent phenylephrine as shown in red color and total phenylephrine as shown in blue color, following a marketed single dose 10-milligram oral phenylephrine product, are compared in this slide. The PK profile on the left is on a log scale and PK profile on the right is on

a linear scale.

The table listed here compared the systemic exposure between the parent and total phenylephrine. The C_{max} of parent phenylephrine is only about 0.3 percent of the value of the total phenylephrine and the AUC of phenylephrine is only about 0.1 percent or the value of total phenylephrine. In addition, the half-life of parent phenylephrine is also shorter than the total phenylephrine.

We have compared in vitro and in vivo phenylephrine concentrations in the previous slides. Next, let's examine the in vivo pharmacology effect of phenylephrine following the oral administration route. Here, the in vivo pharmacology was measured as systemic alpha-1 adrenergic activity, mainly the systolic blood pressure change from baseline as an indicator.

In 2015, McNeil Consumer Healthcare published a phenylephrine clinical trial, which was a randomized, double-blind, placebo-controlled, single-dose, dose-ranging crossover study to

evaluate the PK and PD, following up to 30-milligram oral dose of phenylephrine hydrochloride immediate-release tablets in 28 healthy subjects. The PK profiles, as shown on the left, demonstrated a roughly dose-proportional increase of parent phenylephrine systemic exposure across a 3-fold range. The PD profiles, as shown on the right, demonstrate that the mean maximum systolic blood pressure increased approximately 4 millimeter mercury from the baseline following the 10-milligram to 30-milligram oral dose of phenylephrine at about 30 minutes post-dose. By the way, the T_{max} of phenylephrine following oral dose is about 30 minutes.

The magnitude of systolic blood pressure increased from baseline following 10-milligram oral dose of phenylephrine is considered relatively small. The duration of the systolic blood pressure peak is also short, less than 1 hour. In addition, there's no clear dose-response relationship observed for this small and transient increase of systolic blood pressure across a 3-fold dose range.

On the contrary, a clear dose or exposure-response relationship was observed for phenylephrine following 6 minutes continuous IV infusion in healthy subjects from a literature report. Here, the left panel is the parent phenylephrine plasma concentration at a steady state following the IV infusion, and the right panel is the blood pressure profile at a steady state following the IV infusion.

When phenylephrine is infused with the lowest dose in this study, 0.5 microgram per kilogram body weight per minute, there was an increase of 3-millimeter mercury of systolic blood pressure from the baseline at a steady state, with parent phenylephrine plasma concentration around 3 nanogram per mL. The result is consistent with oral phenylephrine PK and PD results observed from the previous slide.

As we have mentioned, following IV infusion at a steady state, 3 nanogram per mL of parent phenylephrine concentration resulted in 3-millimeter mercury of systolic blood pressure

increase. Here, following an oral administration, a parent phenylephrine C_{max} value ranges from 1.4 to 4.5 milligram per mL, which results in 4-millimeter mercury increase of systolic blood pressure. The results are consistent with each other.

Of note, at this level, the exposure of phenylephrine major metabolites, following a 10-milligram oral dose, is estimated to be at least 40-fold higher than following the 6 minutes 0.5 microgram per kilo per minute IV infusion; yet, we did not observe any substantial change of blood pressure from baseline compared to the IV infusion, which is consistent with the in vitro pharmacology results for phenylephrine metabolites.

Let's go back to this IV infusion study again. It takes an infusion rate of 1 microgram per kilo per minute to reach a steady state concentration of approximately 10 nanogram per mL of parent phenylephrine to achieve about 10-millimeter mercury increase of systolic blood pressure from baseline, and this 1 microgram per kilo per minute infusion rate is within the range

of the approved IV phenylephrine dose for the treatment of hypotension, resulting primarily from vasodilation in the setting of anesthesia. Therefore, we consider the systemic alpha-1 adrenergic agonistic effect, about 10 millimeter mercury increase of systolic blood pressure in healthy subjects, with parent phenylephrine plasma concentration of 10 nanogram per mL are both pharmacologically and clinically meaningful.

Based on the PK and PD results and the relationship following the IV infusion of phenylephrine, it is estimated that an oral dose of approximately 100 milligram is needed to achieve a C_{max} value around 10 nanogram per mL in order to achieve about a 10-millimeter mercury increase of systolic blood pressure from baseline. That's about 10 times of the currently monographed oral dose of phenylephrine.

Indeed, later Dr. Starke will display more systolic blood pressure results from some early clinical trials in his section. These results demonstrated that 100 milligrams of oral

phenylephrine not only distinguished its effect on the magnitude of the systolic blood pressure increase from baseline, but also the sustainability of this increase. However, just to clarify, FDA neither suggests 100 milligrams is a proper oral dose for treating nasal congestion, nor indicates that there is any clinical evidence to support this dose.

Although we acknowledge the comments from the 2007 AC meeting, which recommended higher oral doses of phenylephrine be explored for treating nasal congestion, a noticeably sustained increase of blood pressure following a higher oral dose of phenylephrine, if observed, will certainly raise safety concerns.

We acknowledge that there's no clinical trial conducted to translate or compare the real-time systemic alpha-1 adrenergic activity of phenylephrine on blood pressure to its nasal decongestive effect in patients with nasal congestion. However, there are no in vivo or in vitro results published to demonstrate that the

alpha-1 adrenergic receptors in nasal mucosa is more sensitive than in systemic circulation in humans; neither are studies conducted to show that phenylephrine can be enriched in nasal mucosa following the oral administration route.

Let's take this translatability question from a different angle by looking at the marketed phenylephrine concentrations in the monographed intranasal phenylephrine products. These concentrations ranged from 0.125 percent to 1 percent or 1.25 to 10 milligram per mL. These monographed phenylephrine concentrations in the nasal solution, to be directly applied to the nasal mucosa, is at least 1,000,000-fold higher than the parent phenylephrine plasma C_{max} value following the monographed oral dose.

The 1,000,000-fold difference of concentrations can be roughly demonstrated by taking just one drop of phenylephrine intranasal product and put it into 10 gallons of water, and you mix it very well; note the phenylephrine concentration in that 10 gallons of water is

roughly the plasma phenylephrine C_{max} value following the monograph of 10-milligram oral dose.

We acknowledge that 1.25 to 10 milligram per mL phenylephrine concentration in nasal solution for treating nasal congestion is based on expert opinions, and that the therapeutic concentrations for intranasal products were not well explored in the past as well. However, the fact that there's a 1,000,000-fold drug concentration difference between the intranasal and oral administering route for the same indications, with the same target tissue, which is nasal mucosa, provides the useful context in which to consider the potential efficacious dose range for oral phenylephrine.

From literature reports, we know that oral phenylephrine can cause substantial increase of blood pressure at a concentration far below 1.25 milligram per mL. For example, a study reported that following 250 milligram oral dose of phenylephrine, which is 25 times the monographed 10-milligram oral dose, the mean systolic blood pressure increased by approximately 30 millimeter

mercury.

Here are some take-away values. The plasma C_{max} value of parent phenylephrine is approximately 1 nanogram per mL following the monograph to 10-milligram oral dose. It is lower than the in vitro alpha-1 adrenergic agonistic EC_{50} values, and it is about 1 magnitude lower than the concentration following the IV dose within the approved dose range of phenylephrine for treating hypotension, and it is lower than approximately 1 millionth the value of phenylephrine concentration of the monographed phenylephrine nasal solution products indicated for nasal congestion. Of note, there's a typo at the end of this slide, which the values in the parentheses of the footnote number 3 should be 0.125 percent to 1 percent, not 0.125 percent to 0.5 percent.

In conclusion, following a 10 milligram oral dose of phenylephrine, the oral relative availability of parent phenylephrine is less than 1 percent. Meanwhile, although phenylephrine major metabolites have higher bioavailability, they do

not have detectable alpha-1 adrenergic agonistic activity both in vitro and in vivo. The systemic alpha-1 adrenergic activity, as measured by systolic blood pressure and increases from baseline following the 10-milligram oral dose, is considered relatively small, only about 4 millimeter mercury. We acknowledge there's a lack of dedicated clinical data to elucidate the translatability of this systemic alpha-1 adrenergic activity to local nasal decongestive effect; however, we do have clinical trial data looking directly at the efficacy of phenylephrine on nasal congestion, which Dr. Starke will present in detail in the next section.

Last but not least, the optimal dosing frequency of oral phenylephrine for the treatment of nasal congestion has not been sufficiently explored in the past, as the half-life of parent phenylephrine is only about 1.5 hours in the systemic circulation, whereas the monographed dosing interval for oral phenylephrine is 4 hours. This slide concludes my presentation, and I'll pass the podium to Dr. Starke.

FDA Presentation - Peter Starke

DR. STARKE: Thank you, Dr. Ren.

Good morning. I'm Dr. Peter Starke, and I will present the clinical data regarding the efficacy and safety of orally administered phenylephrine as a nasal decongestant. Before beginning, let me briefly introduce myself. I'm a pediatrician. I was in practice for over 22 years before joining the Pulmonary Allergy -- and now the Pulmonary Allergy and Critical Care division -- in 2000. I served in that division for over 18 years, until I retired in 2018. I've returned in January of 2022 to lead the clinical review group, looking at issues with the cough, cold, allergy, bronchodilator, and antiasthmatic over-the-counter monograph also known as the Cough Cold or CCABA monograph.

Today, you're going to hear about two sets of data, one that was used to establish the GRASE status of oral phenylephrine, which was reviewed for the 1976 ANPR and finalized in the final decongestant monograph in 1994, and the second set,

which starts after that time but really begins with presentations made by industry at the 2007 advisory committee meeting.

The two sets of data are markedly different, and a lot has changed since the original DESI panel reviewed the data and made recommendations to the agency in 1976. In fact, changes to drug development, clinical trial design, and clinical review practices would be a whole talk in and of itself, but the science has also advanced, and this talk will focus on the efficacy and safety data through the lens of current best clinical drug development and review practices.

I will start by briefly summarizing the scope of the new database, including summarizing what was presented at the 2007 advisory committee meeting, after which I will discuss the results from the new clinical trials. However, a full understanding of the new data can only be accomplished within the context of understanding all of the available data, including the original studies, which were also discussed at the 2007

advisory committee meeting, so I will present the original data as well.

First, the scope of the new database, this table summarizes the database of clinical trials with new data. There were five trials starting with two EEU, or environmental exposure unit studies, that were discussed by Schering-Plough Merck at the 2007 Nonprescription Drug Advisory Committee meeting, and three large clinical trials conducted since then. I will be presenting each of these studies as we go through the data. Schering-Plough and Merck worked together on the various parts of this program and merged in 2009, so for convenience, I'll be referring to the clinical program interchangeably as Schering-Plough Merck or just Merck.

This table summarizes the number of subjects randomized to each dose. The first trial was a crossover study and the rest use a parallel group design. First, some historical context; as you heard before, in 2007, the agency received a citizen petition requesting that we amend the

dosage of both oral phenylephrine salts by increasing the maximum dosage for patients 12 years of age and older and to withdraw approval for use in children less than 12 years of age. The agency decided to hold an advisory committee meeting in December of that year to discuss the scientific merits of whether higher doses of oral phenylephrine would be warranted in adolescents and adults.

The second proposal to remove approval for use under 12 years of age was not discussed because the use of cough and cold medicines in the over-the-counter, cough-cold monograph had been discussed at a Joint Nonprescription Drug and Pediatric Advisory Committee meeting held in October of that year; and by the way, I was at that meeting, and I presented at that meeting.

This slide summarizes the meeting and recommendations. Both the petitioners and industry presented meta-analysis of the original studies. Additionally, an FDA statistician looked at all the studies and both meta-analyses. At that meaning,

Schering-Plough and Schering-Plough Merck presented, quote/unquote, "new pharmacology and bioavailability data" that had not been available prior to that time, along with two environmental exposure unit, or EEU, studies, that showed no efficacy at monographed doses.

The advisory committee recommended that more clinical data be obtained to evaluate higher oral doses of phenylephrine than the monographed dose. They also recommended that symptom scores be used rather than nasal inspiratory resistance, or NIR, which is the primary endpoint that had been used in all the original studies.

Schering-Plough and Merck presented in subsequently published receptor binding, clinical pharmacology, and clinical data at the 2007 advisory committee meeting. You heard about the receptor binding and clinical pharmacology data from Dr. Ren. I want to put Schering-Plough and Schering-Plough Merck's advisory committee presentations into some perspective.

This slide summarizes the publicly available

information about several Schering-Plough Merck programs that involved the use of oral phenylephrine. After conducting receptor binding and PK studies, Schering-Plough and Merck performed the two environmental exposure unit studies that were reported at the 2007 advisory committee meeting. Although the EEU studies were conducted for entirely different purposes, the results showed a lack of efficacy for oral phenylephrine at monographed doses, after which Merck performed two large clinical trials, one each for immediate-release and extended-release products.

The publication for one of those studies, the immediate-release dose-ranging study, states that Merck first conducted safety studies and identified 40 milligrams as a safe dose to study, and the publication for the 30-milligram extended-release product reports that they had conducted a bioequivalence study that failed to match the exposure from three 10-milligram tablets dosed every 4 hours, with a 30-milligram extended-release product.

These are the Schering-Plough Merck trials, two EEU studies followed by the two large clinical trials. I'll cover the two EEU studies first. EEU studies are considered proof-of-concept, pharmacodynamic, or early phase 2 studies. They are often used in the early evaluation of an allergic rhinitis drug to establish whether a dose might be effective before proceeding to larger dose-finding studies. Subjects with seasonal allergic rhinitis, or SAR, are first primed by multiple exposures to pollen in the EEU chamber, and when symptoms are sufficient, are treated and observed for the drug effect.

As I am sure you're aware, SAR includes the symptom of nasal congestion. Schering-Plough Merck performed two such studies. One compared phenylephrine with pseudoephedrine and placebo, and one compared phenylephrine with the test product and placebo. The primary efficacy assessment in both studies was changed from baseline and average nasal congestion scores over 6 hours, although nasal airway resistance and/or peak nasal

inspiratory flow, or PNIF, were also evaluated. In both studies, phenylephrine was no more effective than placebo.

This slide describes the first study which compared a 12-milligram dose of phenylephrine, the European oral dose, with 60 milligrams of pseudoephedrine and placebo and 39 subjects with SAR. It was a randomized, investigator-blinded, single-dose, 3-way crossover study. It was conducted in January of 2006, shortly after the Combat Methamphetamine Act was passed and several months before the act actually took effect. As such, the publication for this trial infers that it was conducted to help transition from pseudoephedrine to phenylephrine-containing products.

Here are the results. Focus on the left, where nasal congestion scores are plotted over time. There was no difference between phenylephrine and placebo for nasal congestion scores, whereas pseudoephedrine showed a significant effect, as evidenced by a sustained

decrease in congestion scores. On the right is nasal rhinometry with a positive score denoting improvement. Pseudoephedrine showed an effect, whereas phenylephrine and placebo did not.

CHPA has raised concern over several issues with this study. First, the primary endpoint was out to 6 hours, whereas the monographed phenylephrine dosing interval is every 4 hours. But you can see visually on the left-hand side that if one made a cutoff at 4 hours, it would not have changed the results. In fact, it's likely that the primary comparison for nasal symptoms scores between pseudoephedrine and placebo would have been statistically stronger, and that the same conclusion would have been reached for each of the treatment comparisons with placebo.

Second, CHPA argues that because the study was only investigator blinded and subjects knew what treatments they might be getting, there might have been a crossover effect for those subjects who received pseudoephedrine prior to receiving placebo, thereby creating a positive bias in those

subjects. However, the same might be said for the arm crossed over from phenylephrine to placebo if phenylephrine had shown a positive effect, suggesting that a crossover effect did not significantly bias results against phenylephrine.

Now, this slide shows the same nasal rhinometry on the right but peak inspiratory flow, or PNIF, on the left. Again, pseudoephedrine showed a significant effect, whereas phenylephrine and placebo did not. In fact, if you look, PNIF tracks better with nasal congestion symptoms than does NAR.

This is Schering-Plough's slide from the 2007 advisory committee meeting showing the mean change in nasal congestion scores for each treatment, phenylephrine, pseudoephedrine in the middle, and placebo on the right. As you will see in tiny print on the bottom left, which I expanded for visibility, the only comparison that was statistically significant was pseudoephedrine versus placebo.

This is the second study. It was a large

randomized, double-blind, double-dummy, placebo-controlled, single-dose, parallel group study in 379 patients with SAR to ragweed. It was conducted primarily to evaluate a test product, loratadine combined with montelukast. As such, it included phenylephrine as a so-called positive control.

Here are the results. These figures are taken directly from Schering-Plough Merck's presentation. On the left are mean changes from baseline and congestion symptoms scores with the test product in blue, phenylephrine in green, and placebo in gray. Within the boxes are the N's for each treatment arm, which were substantial. On the right are mean changes in symptom scores over time. There was no statistically significant difference between phenylephrine and placebo in this study.

Here is Schering-Plough's conclusions that they shared at the advisory committee meeting, and I'm quoting. "A single dose of oral pseudoephedrine 60 milligrams showed the expected decongestant response, mainly in symptoms and airflow, compared to placebo. A single oral dose

of phenylephrine 10 or 12 milligrams overall showed no decongestant response compared to placebo, and that was replicated in two studies."

There were three large trials conducted since the 2007 advisory committee, two by Merck conducted between 2011 and '12 and published in 2015 and '16, and one by Johnson & Johnson conducted in 2017 to '18; the Merck clinical trials first.

Merck's two large clinical trials were both conducted in subjects with SAR. One was a phase 2 dose-ranging study that evaluated 10, 20, 30, and 40 milligrams of immediate-release phenylephrine versus placebo, and one evaluated a 30-milligram extended-release product versus placebo using an extended-release formulation, which we know provided a higher systemic exposure than three 10-milligram immediate-release doses dosed every 4 hours. The results of both trials were published in peer reviewed journals and at clinicaltrials.gov.

The size and primary endpoint for these

trials were reasonable and similar to phase 2 and 3 trials for drug registration of antihistamines and intranasal products for allergic rhinitis. I will also note that seasonal allergic rhinitis provides a more stable environment than colds, which is the population evaluated in all but one of the original studies, although that's primarily because catching subjects at the right moment in the cold prevents an enrollment issue.

Nasal congestion was rated twice daily on a 4.0 to 3 scale following the FDA guidance on development of drugs for allergic rhinitis, with the primary endpoint being change in reflective nasal symptoms scores over one week of treatment. Neither trial showed efficacy of any dose of phenylephrine compared with placebo, and no meaningful safety issues were noted.

The publications for the two large trials state that Merck supported the dosing used in these trials with safety studies. The publication for the IR 10-milligram to 40-milligram dose-ranging trial reports that those studies showed support for

up to 40 milligrams, the highest dose studied; however, those studies were never published, so we do not have the results to share with you.

What you see summarized in this slide is a 7-day ambulatory safety study that Merck conducted as part of drug development for the 30-milligram extended-release product. The primary outcome measure was average systolic blood pressure over a 5-hour range around the time of maximal concentration or T_{max}. No meaningful differences in systolic blood pressure were noted for either 30-milligram extended release or placebo.

First, the dose-ranging trial. This trial was published, and the results are also on clinicaltrials.gov. It was a multicenter, randomized, dummied but only partially blinded, placebo-controlled, 5-arm, parallel group trial conducted in healthy adults with SAR caused by spring allergens. All subjects received background treatment of the antihistamine loratadine 10 milligrams, which had previously been demonstrated in two factorially designed clinical

trials to have no effect on congestion, and the publication references the two publications for those trials.

After a 4-day baseline run-in period, all subjects were dosed with immediate-release phenylephrine every 4 hours for 1 week. The reason it was only partially blinded is that they used a similar but not identical placebo, but the fact that the study was placebo dummied, along with the partial blinding, would have made it more difficult for a subject to guess which dose they might have been randomized to receive. That said, if a subject did guess at their treatment allocation, it would likely have favored finding an effect for phenylephrine because there were 4 phenylephrine arms and only one placebo arm, meaning there was a 4-to-1 chance they might think they were taking an active treatment.

The primary endpoint was mean change from baseline in daily reflective nasal congestion scores over the treatment period. 539 were randomized and 519, almost 96 percent, completed

the trial. In the blue boxes, you see the N's for each treatment group, which were quite reasonable and far larger than in any of the original studies. The treatment groups were comparable.

In retrospect, we are aware that there's some potential limitations to the design of this study. First, it was only partially blinded, although I've explained why that should not have mattered. Second, it did not include a positive control, which would have been ideal. That said, based on our review, we consider this trial to have been adequately designed and conducted, and we do not believe that the limitations I mentioned detract from the interpretation of the results.

Here you see the results shown graphically over the course of the trial with mean reflective nasal symptoms scores on the Y-axis on the 4 days before and the 7 days after randomization on the X-axis. You also see the number of subjects in each treatment group on the top right. Note that baseline symptoms were about 2.4 to 2.5, which is in the moderate range. Not only were there no

statistically significant differences between any oral phenylephrine dose and placebo, there were no meaningful differences between doses.

Now, the Merck extended-release trial. This trial was published, and the results are available at clinicaltrials.gov. It was a phase 3 trial performed after a bioavailability study failed to show bioequivalence to, and with higher systemic exposure than three 10-milligram immediately-released phenylephrine tablets. It was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, 2-arm, parallel group design that compared a 30-milligram modified-release phenylephrine with placebo.

This is the largest trial ever conducted to evaluate the efficacy of phenylephrine, and with enrollment of 287 and 88 subjects in the respective arms, it was comparable to what one might expect to see in phase 3 allergic rhinitis trials. The treatment was twice daily for 7 days, with no background treatment except loratadine as an as-needed rescue. The primary endpoint was mean

change from baseline in daily nasal congestion scores over the treatment period. 575 subjects were randomized and 574 completed the study. Treatment groups were comparable.

Based on our review, we consider this trial to have all the features of an adequately designed and well-conducted trial. As such, this trial provides the best information available to date regarding the efficacy of oral phenylephrine.

Here are the results for the primary endpoint of mean change from baseline in reflective nasal congestion scores over 7 days. On the left you see placebo in blue and the modified or extended-release phenylephrine in red. There was a similar response to each with no statistically significant difference between the two treatments. On the right, you see the results expressed in tabular format with baseline and mean change shown.

I used the data available at clinicaltrials.gov to make this graphical representation of the mean daily reflective nasal congestion scores over the course of the study,

with nasal congestion scores on the Y-axis and time starting with baseline on the X-axis. Again, placebo is in blue and extended-release phenylephrine is in red. You see no meaningful separation of the two at any time point over the course of the trial.

Now, those two trials were conducted by Merck in subjects with allergic rhinitis. We also have available the results of a subject of the study conducted by Johnson & Johnson in subjects with a common cold. This study was conducted in Canada during the 2017-18 cold season and published only at clinicaltrials.gov. It was a randomized, double-blind, double dummy, placebo-controlled, 3-arm, parallel group trial in adults with nasal congestion due to the common cold about 72 hours into symptoms. Treatments were a 30-milligram, extended-release phenylephrine tablet taken twice daily, 2 doses 12 hours apart, and the European dose of phenylephrine 12 milligrams as an IR capsule taken 4 times daily, 4 doses 4 hours apart, and placebo. Again, all treatments were

double-dummied for blinding purposes.

Assessments were reflective nasal congestion severity scores, or NCSS, assessed on an 8-point 0-to-7 scale where 0 equals none and 7 equals severe, and performed at baseline and at 2, 4, 6, 8, 10, 12, and 24 hours after the first dose. While we do not have PK data from this particular extended-release formulation, note that the trial included both their extended-release formulation and the 12-milligram immediate-release product.

The primary endpoint was mean change from baseline in NCSS over 0-to-12 hours after the first dose analyzed for the ITT population using an ANOVA model with treatment group, study center, and baseline nasal scores as factors. Demographics were similar between the three arms, and no adverse events were reported. Unfortunately, while Johnson & Johnson planned to enroll 450 subjects, they were unable to enroll the full number and terminated the study at the end of the cold season, having enrolled only 193 subjects. So while it's still a relatively large study, it was not nearly

as large as originally contemplated. Nevertheless, we consider this the best data available for use of oral phenylephrine as a decongestant in the setting of subjects with colds.

Here are the results, which I took from clinicaltrials.gov and converted to a figure, which you see on the left and a tabular format on the right. Placebo is in blue, immediate release is in red, and the extended-release formulation is in green. There were no meaningful differences between the three treatment groups and the comparisons.

The comparisons between either phenylephrine treatment and placebo were not statistically significant, one thing to note and one correction on the slide. First, the correction. The mean change results from the table includes standard deviation, or SD, in parentheses, when in fact it should have been designated as standard error or SE. The standard deviation should be much larger, around 1.25 in this case.

Second, note that the results are expressed

as positive numbers for all three treatment groups, which either suggests that the results are expressed as absolute change or that everyone got worse, because based on the scoring system, higher numbers would reflect more severe congestion scores, so I suspect it was expressed as absolute change.

Here you see a graphical representation of those results which I created from information available at clinicaltrials.gov. What appears to be absolute change from baseline is on the Y-axis and time is on the X-axis. As you see, there were no meaningful differences between treatments at any time point.

Our statisticians created this slide which summarizes the treatment difference in change in nasal congestion scores for each dose in each of the four published studies from Merck. The studies are color coded by trial. As I showed you in a previous slide, the Horak 2009 study included pseudoephedrine, which is marked with a blue arrow, and showed the expected positive result. A

confidence interval was not available for the Day study in green, and the J&J trial was not included in this plot because it used a variation on nasal symptom scoring, whereas all four of the Merck trials used the same scoring.

Note the narrow confidence intervals around the results with all of the confidence intervals for phenylephrine versus placebo comparisons overlapping zero. The only result that was significant was the comparison between pseudoephedrine and placebo. Also shown in the next-to-the-bottom line are the results of a comparison that our statisticians performed with placebo when the results for all 4-to-40 milligram phenylephrine doses in the dose-ranging study are pooled.

I turn now to the data that supported the GRASE recommendation in the monograph. First, I will discuss the meta-analysis of the original data that were presented at the 2007 advisory committee meeting, after which I will discuss the studies themselves, but through the lens of current

clinical trial design and review guidance.

At the advisory committee meeting, the petitioners and industry presented meta-analyses, each of which used a different number of the original studies and each of which used different statistical methodology. Not unexpectedly, the petitioners' analysis did not confirm the original findings, whereas the industry analysis did. But what do the meta analyses actually tell us about the studies themselves?

Here you see a summary slide of the petitioners' meta-analysis. It shows all the studies that they included. One of their key findings was that two studies performed at the Elizabeth Biochemical lab's study site for Sterling-Winthrop, the manufacturer of Neo-Synephrine, were the two most positive studies. You will see this both visually and in a column showing the percent NAR difference. They also suggested that not only did the results of those two studies drive the results of the meta-analysis, these two studies were outliers when compared with

the rest. A third study also performed on behalf of Sterling-Winthrop, but at a different laboratory, Cintest, was also positive and also appeared to drive the results.

The FDA statistician, Dr. Lin, reviewed both sets of meta-analyses and pointed out the two included different studies and different analyses of the nasal airway resistance endpoints than had been used in the original studies. He also noted that NAR is no longer accepted by the agency as a primary endpoint, and we'll get to that later. When he looked at the studies themselves, he found evidence of a treatment by study site interaction which both indicated heterogeneity and limited poolability, but that was as far as he went in interpreting the variability of the results. His final assessment was that neither meta-analysis was conclusive.

I turn now to our reassessment of the original studies through today's review lens, but I want to be clear that in doing so, I am not in any way denigrating the fine work that the original

panel did. They provided the agency with recommendations based on their best assessment of the data available to them at the time. It's just that the science has changed in the interim.

This slide summarizes the safety data available to the DESI panel. Sixteen studies were reviewed for safety, with doses mostly between 5 and 60 milligrams, but several up to 100 milligrams. The graphic on the right shows that the pharmacodynamic effects on blood pressure were considered inconsistent and transient until close to 100 milligrams, with no meaningful cardiovascular side effects at the monographed 10-milligram dose. There are no other safety issues noted, and for here on, I will only focus on efficacy.

For efficacy, 14 studies were considered with oral doses up to 40 milligrams. All but one study were in subjects with colds. All used as the primary endpoint nasal airway resistance, or NAR, as measured by rhinomanometry. Symptoms were secondary endpoints, and they generally were not

considered if the primary endpoint was not successful. Most all evaluated pharmacodynamic endpoints of blood pressure and heart rate.

Here's the breakdown of those 14 studies broken down by parallel or crossover design; along with the study, a brief description, and the results. One was a parallel group study, the results of which were considered positive, and the remaining 13 were crossover studies of which six were considered as positive. Two studies, one from the University of Maryland and one preliminary study from Sterling-Winthrop, had no interpretable or useful efficacy data, so we did not have any data to review. So that leaves 12, the parallel group BEI study, 10 Sterling-Winthrop crossover studies, and a crossover study from Columbia University, and we'll discuss the BEI 1025 study next.

The BEI 1025 study was performed by Whitehall Laboratories. It was the largest study and the only study with a parallel group design. It's also the only study not conducted by

Sterling-Winthrop that was considered to be positive. It was a double-blind, placebo-controlled, parallel group design in 200 subjects with the common cold. All subjects received 4 doses of 10 milligrams of phenylephrine hydrochloride or placebo over 12 hours. Whereas all 200 subjects, 100 per arm, were evaluated for symptoms, only 50 subjects, 25 per arm, received rhinometry, which was the primary endpoint. These measurements were performed at 0, 15, 30, 60, and 120 minutes after the first dose.

As you see in the graphic on the right, no differences were seen in systolic or diastolic blood pressure, implying that a pharmacodynamic effect on blood pressure was not seen in this study. However, they did report changes in both NAR, as well as for symptoms of nasal congestion, runny nose, and sneezing, which they judged to be significant compared with placebo, with no improvements in the symptoms of cough or muscle ache.

That said, there were issues with the study

including that the methodology to reduce bias on the scoring methodology for symptoms were not specified, and no adjustments were made for multiplicity. In fact, the protocol was referred to in the study report, but was never submitted to the docket.

There were also significant issues in interpreting symptom results, which were secondary endpoints. While it appears that baseline symptoms were rated on a scale of 5 from mild to severe, it appears that improvement may have been rated on the 0-to-2 scale, with 0 being no change and 2 being much improved, and that this evaluation was performed by the subjects and investigators. However, we do not know the frequency of the scoring, whether it was instantaneous or reflective, and how much weight was placed on investigator judgment. That said, one must ask why a nasal decongestant, which would only be expected to help obstructive congestion symptoms, would also help runny nose or sneezing symptoms, which throws suspicion on the results of the obstructive

symptoms.

Here you see the results that were reported for NAR over 2 hours following the first dose. The study used percent change from baseline as the primary endpoint, which is on the right, and absolute change is on the left and present reduction at each time point as shown in the box on the right.

Next is the so-called negative study from Columbia University. This study was conducted over several years, and the results were published in several journals as this study progressed, both by Bickerman and Rogers. It was performed at Columbia University. It was a randomized, double-blind, placebo-controlled, crossover study conducted in 57 patients with reversible non-atopic nasal congestion.

Now, the ANPR only reported on 20 of these subjects, whereas in this slide, I'm showing the full study results. The investigator had spent several years studying and developing new methodology to have more accurate nasal airway

resistance measurements, including designing their own measurement instrument based on naval diving equipment. They had also looked at 47 healthy volunteers over an extended period of time, including, over the course of the day, between each nostril and when they became ill with a cold, so they had a significant baseline of information upon which to evaluate drug treatments.

Treatments included placebo, pseudoephedrine 60 milligrams, phenylpropanolamine 40 milligrams, and 3 doses of phenylephrine, 10, 20, and 40 milligrams. As you see in the graphic on the right, there was no change in NAR for placebo or the 10-milligram phenylephrine dose, but significant reductions were noted for pseudoephedrine and phenylpropanolamine. Not shown in the graphic are the 20- and 40-milligram doses, which are reported as having been negative as well. It's also important to note that this study contained not one, but two positive controls that clearly showed an effect, whereas both placebo and 3 doses of phenylephrine did not.

Now we come to the 10 studies conducted by Sterling-Winthrop of which six were considered positive and four were negative, and the Sterling-Winthrop studies were conducted at three different sites, but all used essentially the same protocol and endpoints. They were randomized, double-blind, placebo-controlled, 2-way crossover studies in subjects with colds. The primary endpoint was nasal airway resistance and the secondary endpoint was symptoms, which were generally not considered if NAR was not positive. That said, there was no clear delineation in the study reports for how symptoms results were collected.

This table shows the number of completed subjects in the 10 studies. On the left, you see the site names and the study numbers, which are grouped by site rather than in chronological order. Studies considered positive for NAR results are in red font. Across the top are the various phenylephrine doses studied, as well as doses of several positive controls.

All subjects were crossed over with placebo, and the number of completed subjects for each study dose are shown within the table itself. The monographed 10-milligram dose column is shown in pink. I want to point out two things here. First, note the very small number of subjects studied at each site and each dose, especially when compared with the table I showed for the new trials. Second, all the studies performed at the Elizabeth study site were positive, as were all the doses studied. That is the group of five studies listed first, and then the second group representing two other study sites. Neither of the two studies at the Huntingdon site and only one of the three studies at the Cintest site were positive.

One has to ask the question of why that is. At least part of the answer is that there is no standardization of the NAR methodology, resulting in a procedure that's highly technician and equipment dependent. This may be the reason that the Huntingdon 1 study, listed immediately below the five Elizabeth studies, also found no effect

for phenylpropanolamine when it should have shown one. You also see that doses up to 25 milligrams also failed at several of those sites, whereas they were positive at the Elizabeth site, again reinforcing that the procedure is not sufficiently standardized such that it is difficult to transport from one site to another. That said, none of the studies documented an effect on systolic blood pressure, suggesting that the alpha-1 receptors were not activated by any of the phenylephrine doses studied.

Further, two of the Elizabeth studies, 4 and 5, were terminated early due to insufficient enrollment at the end of the cold season, and so the number of subjects in these two studies are even more limited than in the other studies. And I might add, it's Elizabeth 2, 5, and Cintest 1 that drove that original meta-analysis of the citizen petitioners, the slide that I showed you earlier from the citizen petitioners.

I will not show all of the results from these studies, only this one slide, which compares

the results of the 10-milligram dose in two of the Sterling-Winthrop studies that resulted in markedly different results, Elizabeth 2 on the left and Cintest 3 on the right, and you'll see that Elizabeth 2 was positive and Cintest 3 was negative.

Look at the general curves because the reports used different Y-axes, with objective change from baseline for Elizabeth 2 on the left and change from baseline as a fraction of the reading for Cintest 3 on the right, so they're not directly comparable; yet you can still visually see that there's a vast difference in the curves, which provide some illustration of how different the results were from one study to the next. I will not touch on symptoms because the study reports are such that the manner in which they were captured is entirely opaque.

Going back to the DESI panel's conclusions, they concluded that the data were, quote, "not strongly indicative of efficacy," unquote, but in the absence of the safety issue, they recommended

that the 10-milligram dose, which was the marketed oral dose, be considered GRASE. That said, they knew there were significant failed studies and that the positive data were weak. They also knew that it takes an oral dose of close to 100 milligrams to have a consistent pharmacodynamic effect on systolic blood pressure, while they did not know what we now know about the bioavailability profile, namely less than 1 percent, data that were not available until better assays were developed around the turn of this century.

Now, I will discuss our evaluation of those studies. The first thing to say here is that these studies were performed in a much different era, before ICH, or the International Council for Harmonisation, was established or guidances for how to design and conduct clinical trials were published. But I want to be really clear about this. Just because these studies predate those guidances does not make them bad or unacceptable. However, in this case we have a reason to go back and look at these studies, and when we do, we look

through the new lens, and we see anomalies and huge variability in the results that cannot be easily explained.

The study reports are not specific and systematic, and the protocols were never submitted to the docket. So it's impossible to verify that the design and conduct of these studies were sufficient to prevent the introduction of unintended bias. And more specifically, it's unclear if appropriate study monitoring and auditing occurred, procedures that might have identified the issues that we see with the data anomalies.

I will also add that in these studies, clinical symptoms are poorly documented as to how and when they were collected or scored, and by whom, subject or investigator. Therefore, they cannot be relied on to provide helpful information, so one has no choice but to rely on the primary endpoint, which was NAR.

There are three problems with this approach. One, the NAR procedure isn't standardized. It's

highly variable and is subject to numerous methodological issues related to the measurement tools, measurement technique, and technician training and competence. This may explain why there were so many failed studies and the lack of reproducibility at and between study sites.

Two, the endpoint of NAR was never validated, meaning that we have no information that allows us to translate changes in NAR to a clinical benefit in nasal congestion, so there is no information on clinical relevance. And three, and probably the most important, NAR is a surrogate endpoint, and the use of surrogate endpoints is fine when we don't have a way to directly measure the effect -- there are lots of examples of that -- but in this case we have a validated and accepted endpoint of nasal congestion symptom scoring that has been used for the last 30 plus years, and phenylephrine is monographed to treat the symptom of nasal congestion. As a result, FDA would no longer accept NAR because we have available an accepted way to directly assess the

symptom itself.

I addressed the issue of blinding protocols and bias in the previous slide, so I'll skip the first bullet. All were single-center studies and all had extremely small N's with no sample size calculations, no statistical analyses plans, and no controls for multiplicity. Further, as I showed you before, two of the five positive studies from the Elizabeth site ended early due to enrollment issues. The bottom line is that none of the original studies stand up to modern standards of study design or conduct.

As we reviewed the 10 Sterling-Winthrop studies, we also noted, as had the petitioners and Dr. Lin in 2007, that the findings at the Elizabeth site were highly inconsistent with those from the other two study sites. In fact, in retrospect, we found evidence that there may have been data integrity issues at the Elizabeth study site. Some of this evidence was contemporaneous.

First, the study report from the Cintest 2 study notes that after being unable to duplicate

the results from the Elizabeth site, they visited the Elizabeth site to observe the techniques being used and to ensure that they were doing the same, but they did not find any significant differences. Second, after the Huntingdon 1 study was unable to duplicate the Elizabeth results, they performed a standard deviation analysis of the results from all three study sites that had been conducted in studies that have been conducted thus far and compared them with the standard deviation at their own site. The table in the Huntingdon 1 study report shows that the standard deviations at the Elizabeth site were 10 times or more smaller than at the other two sites.

Finally, we also found that the results from the Elizabeth 2 and 5 studies are near textbook perfect. The curves mimic the known PK curve at the time and show no change from baseline in placebo, something that would not be expected based on the study size, variability of the endpoint, and what we now know about the bioavailability of oral phenylephrine. Finally, there was a publication

from 2010 that included a forensic analysis on the last significant digit, which is the tenths column, in Elizabeth studies 2 and 5, which were the most positive studies. For the Elizabeth 2 study, they found an unusual occurrence of the digit 5, which they believe would not have occurred randomly or by chance.

There is one additional study that was published but never submitted to the docket, and was not considered by the DESI panel, but I present it here for completeness sake. This study was published by Cohen in 1972. This appears to be the same author as that of the Whitehall's BEI 1025 study, although it also appears from the notations in the publication that it was supported by Sterling-Winthrop, who provided the study drug and matching placebo, as well as the randomization codes.

It was a randomized, double-blind, placebo-controlled, single-dose, 2-way crossover study in 48 subjects, 16 per arm, who were experiencing cold symptoms. You see the doses of

phenylephrine studied and crossed over with placebo, 10, 15, and 25 milligrams. The primary endpoint was nasal airway resistance, and the secondary endpoint was nasal congestion on a 5-point scale.

That said, this study appears to have the same methodological and statistical issues as I mentioned for all of the other DESI studies. Again, you see no meaningful change in systolic blood pressure with any of the doses and no differences from placebo. Here are the results, which appear to show a positive effect for each dose of phenylephrine in both NAR on the left and nasal congestion scores on the right.

So to summarize, I've shown you two sets of data with differing results. How do we explain the discrepancies between these two sets of data? You heard from Dr. Ren that only the parent, not its metabolites, are active, and that less than 1 percent of an oral dose is active parent phenylephrine, so the drug concentrations, namely C_{max}, following a 10-milligram dose are far less

than the EC_{50} for the alpha-1 adrenergic receptor. This observation indicates that an active pharmacodynamic effect is unlikely to be achieved. The lack of consistent blood pressure effects at 10 milligrams also suggest the lack of alpha adrenergic receptor activation.

Together, both the PK and PD data suggest that much higher doses, perhaps 100 milligrams or more, might be needed to achieve a nasal decongestant effect. We also know that what is systemically bioavailable after a 10-milligram overall dose results in a very short half-life.

We found numerous methodological and statistical issues in the original studies that do not match today's clinical design and conduct standards. The study relied on the surrogate endpoint of NAR, which is not validated, so we have no idea how it relates to clinical relevance, and there were significant inconsistencies in the results between various study centers. Therefore, we do not believe we can generalize the results of these studies to individuals who feel that they

need treatment for congestion.

On the other hand, multiple data sources support that all phenylephrine at monographed doses, as well as extended-release doses of 30 milligrams and IR doses up to 40 milligrams, do not show efficacy. These trials used the accepted direct measurement of nasal symptoms as the endpoint rather than an unvalidated surrogate endpoint that include two environmental exposure unit studies and three large well-designed and conducted clinical trials, two in subjects with SAR and one in subjects with colds. In all of these trials, phenylephrine was shown to be no more effective than placebo.

So in conclusion, we believe that the original studies were methodologically unsound and do not match today's standards. By contrast, we believe that the new data are credible and do not provide evidence that oral phenylephrine is effective as a nasal decongestant. Further, the data suggests that immediate-release doses up to 40 milligrams may not be effective. And finally,

the pharmacodynamic data suggests that higher doses, which have not been fully studied, might present a safety issue because they might be associated with systemic blood pressure and circulatory effects. Thank you for your attention.

FDA Presentation - Tracy Pham

DR. PHAM: Good morning. My name is Tracy Pham. I'm a drug use analyst from the Division of Epidemiology, Office of Surveillance and Epidemiology, FDA. To provide context for today's discussion, I will provide the findings on the sales patterns of OTC oral products containing phenylephrine or pseudoephedrine.

We assessed two databases. One database provides sales from manufacturers and wholesalers to assess use patterns over time since year 2000, and another database provides sales from retail stores to assess the most recent use patterns since year 2018. As outlined on this slide, I will provide findings on the sales from these two databases, their limitations, and the summary of key findings at the end of my presentation.

To gain insight to the use of phenylephrine compared to pseudoephedrine in the context of the Combat Methamphetamine Epidemic Act, we assessed the estimates of bottles and packages of these products sold over time, from 2000 to 2022. To achieve this, we analyzed the manufacturer sale database, which measures volumes of drugs sold from manufacturers and wholesalers to retail and non-retail settings of care in the U.S. Note that although the manufacturer sale database captures OTC sales back to 1992, the data are underestimated because the database captures less than 50 percent of sales of all OTC products.

This graph shows the estimates of bottles and packages of OTC oral products containing phenylephrine or pseudoephedrine sold by manufacturers and wholesalers over time, from 2000 to 2022. As shown by the red line on the figure, pseudoephedrine sales decreased since 2001. As shown by the blue line, phenylephrine sales increased from 2004 to 2009 but declined from 2009 to 2020, before increasing again in 2021 and in

2022.

To gain insight into the current use of phenylephrine compared to pseudoephedrine, we assessed the estimates of bottles and packages of these products sold from U.S. retail stores to consumers from 2018 to 2022. To achieve this, we analyzed the retail sales database, which captures point of sales of OTC drugs to consumers from a panel of retail stores in the U.S. such as grocery, and drug stores, and supercenters. Note that the retail sale data provide a better and comprehensive view of the current sales pattern and should not be directly compared to the manufacturers' sale data shown in the previous slide.

This graph shows the estimates of bottles and packages of OTC oral products containing phenylephrine or pseudoephedrine sold from U.S. retail stores to consumers from 2018 to 2022. As shown by the blue bars, phenylephrine accounted for the majority of retail sales throughout the study period. In 2022, approximately 242 million bottles and packages of phenylephrine were sold to the

consumers compared to 51 million bottles and packages of pseudoephedrine, as shown by the red bars.

From 2018 to 2021, phenylephrine retail sales decreased by 16 percent and pseudoephedrine sales decreased by 19 percent, but from 2021 to 2022, phenylephrine retail sales increased by 31 percent and pseudoephedrine retail sales increased by 16 percent. We also assessed the retail sales in dollars. Note that the sales in dollars represent the price of a manufacturers' pack before the wholesaler markup is applied. Sale patterns in dollars were similar to sale patterns in bottles and packages.

As shown by the blue bars, phenylephrine products accounted for the majority of retail sale dollars throughout the study period. In 2022, the total retail sales of OTC phenylephrine products represented approximately $1.8 billion compared to half a billion dollars of pseudoephedrine products, as shown by the red bars.

On this slide, I would like to restate the

limitations of the databases used for the OTC sale analyses. The manufacturers' sale data are underestimated because the database captures less than 50 percent of sales of all OTC products. The retail sale data provide a better and comprehensive view of the current sale pattern and should not be directly compared to the manufactures' sales because the retail sale database captures direct OTC point of sales from a sample of 80 percent or more retail stores. However, these data may still be underestimated because they do not capture sales activity from internet and phone sales or retail stores such as Costco and convenience stores.

To summarize, phenylephrine had higher proportions of manufacture and retail sales than pseudoephedrine. Since 2018, phenylephrine accounted for the majority of retail sales in both bottles and packages and in sale dollars. Retail sales of phenylephrine and pseudoephedrine decreased from 2018 to 2021 before increasing in 2022. In 2022, phenylephrine retail sales represented $1.8 billion compared to half a billion

dollars of pseudoephedrine retail sales. This concludes my presentation. Thank you.

Clarifying Questions

DR. COYLE: We will now take clarifying questions for the FDA presenters. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can, including a slide title or a slide number if that's available.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of any follow-up questions with, "That is all for my questions," so that we can move on to the next panel member. And as we begin, I would also ask that perhaps if you have several questions, that you might go ahead and ask them one at a time so that everyone has the chance to speak in the available slot before we break for lunch.

So, any clarifying questions from our committee members?

Yes. Dr. Clement, you have the floor.

DR. CLEMENT: Yes. Thank you very much, a very enlightening presentation from all the presenters, incredibly enlightening actually. I had a question if Dr. Bishop is still available, Ben Bishop, on the regulatory history.

DR. MICHELE: So I'll turn the podium to Dr. Ben Bishop.

LCDR BISHOP: Yes. Thank you.

DR. CLEMENT: Yes. Being new to this panel, I'm not intimately familiar with all the legislative activity that's been going on, and you had mentioned the CARES Act as being a significant event. You said in 2020, the start coronavirus CARES Act had a significant impact on the OTC monographs.

Can you explain a little bit more about that and how that impacts our decision when we're looking at the data? Thank you very much.

LCDR BISHOP: Yes. Thank you. I think the

best way to describe it would be to compare the three steps of the previous rulemaking process, which consisted of an advance notice of rulemaking, then the FDA would review any data and comments submitted. The second step consisted of the FDA issuing a tentative proposed rule, or a tentative monograph, and then again allowing for the review of any comments or data to come in, and finally ending with the third step of issuing a final monograph or final rule. This process could take months to years and was very drawn out. The CARES Act provided for the posting of orders, administrative orders, which the FDA can use to post an order for an OTC monograph and streamline that process considerably.

DR. MICHELE: Thank you, Dr. Bishop.

This is Terry Michele, Nonprescription Drugs. Just to augment what Dr. Bishop said, which was a very nice outline of one of the most important changes under the monograph of the CARES Act, I just wanted to highlight one of the things that did not change. The standards for efficacy

did not change under the monograph, nor did the fact that the monograph is still a public process and the data need to be publicly available in order for the public to have the opportunity to comment.

In addition, monograph reform did not change the fact that the monograph represents all of the conditions of use in the monograph, and manufacturers can come to the market without FDA pre-approval as long as they are following those conditions of the monograph. So an efficacy determination is not just for a particular drug product, but for all of the drug products containing oral phenylephrine that follow the conditions of the monograph.

DR. CLEMENT: Thank you very much.

DR. COYLE: Thank you.

I'm going to go ahead and call on Dr. Pisarik. Please go ahead.

DR. PISARIK: This is Paul Pisarik. I just have a question. It seems like alpha adrenergic activity, if it's sufficient, increases blood pressure, and we know that pseudoephedrine works to

help the nasal congestion. By how much does it increase systolic blood pressure? And as an aside, phenylpropanolamine was effective and was taken off the market because of hemorrhagic strokes in women. Did that also increase blood pressure?

DR. MICHELE: Hi. Terry Michele, Nonprescription Drugs. I'm going to turn this over to Dr. Ren to answer that question.

DR. REN: Thank you, Dr. Michele.

Yes, this is Dr. Ren. Let me clarify a little bit. The mechanism for action for pseudoephedrine for treating nasal decongestion is different from the phenylephrine, or even phenylpropanolamine. Pseudoephedrine is a non-selective weak alpha and beta adrenergic agonist. The principal mechanism of pseudoephedrine, if you read from multiple textbooks, it was written that it is considered to replace the noradrenaline from the presynaptic vesicles, which this noradrenaline is released to activate the post-synaptic adrenergic receptors. So that's why the mechanism of action is different.

It's indirect. Unlike phenylephrine, it's directly acting on the alpha adrenergic activity.

Talking about literature reports, any systemic alpha adrenergic activity such as blood pressure measurement following the pseudoephedrine, yes, there are some papers published, but there's no dedicated paper as the one we have presented, which is the dose-ranging study following the phenylephrine that has intensive measuring, like almost more than five even more time points within one hour following the dose administered to exactly follow this blood pressure change.

If you're talking about sporadic study reports about the blood pressure increase from baseline, they are mostly for safety purposes, like after 1 hour or 2 hours let's measure one time or twice the blood pressure, and you won't notice they are having a significant change. I would say it's due to the defect of the data, the time points.

Phenylpropanolamine is also a non-selective adrenergic agonist, but mainly it also works directly on the alpha-1 adrenergic activity. A

couple of years ago, FDA withdrew it because of the hemorrhage adverse event intracranially; therefore, we suspect there could be some systemic alpha adrenergic activity there, play a role there.

DR. PISARIK: Thank you.

DR. COYLE: Thank you, Dr. Ren and Dr. Pisarik.

Dr. Le, please go ahead.

DR. LE: Hi. I have several questions for Dr. Ren and one for Dr. Pham, so I'll start with Dr. Ren.

You've indicated in your pharmacology data that with the recent data, the bioavailability is 1 percent, and that was very clear. I'm curious as to has FDA issued a warning letter, advisory memo, to help pharmacists and clinicians know and be very aware of this data, as most cited, and as you noted in your briefing document, most clinicians and pharmacists would actually cite like about 38 percent bioavailability. So that's my first question.

DR. REN: Okay. I can answer the 38 percent

question, and then I'll defer to Dr. Michele regarding the communication to the public and sponsors regarding this.

Let's go to backup slide, page 12, please. This is a Hengstmann 1982 paper, and came into conclusion that the oral bioavailability for parent phenylephrine was 38 percent. In this paper, the authors compare the parent phenylephrine PK profile following the oral administering route, as shown in white circles in this figure, and PK following the IV infusion, as shown in the black circles in this figure.

The authors calculate the oral bioavailability by dividing the parent phenylephrine AUC value following the oral administration by the AUC value following the IV administration. This is a standard approach to calculate the relative bioavailability, which FDA did the same thing for today's presentation. However, the defect of this paper was the PK sampling scheme, which was not implemented equally between the oral administration and IV

administration.

The first PK sample following the oral administration was collected just minutes after the oral dose, which captured the initial absorption phase following the oral administration route. However, the first PK sample following the IV infusion was not collected until the end of the IV infusion, which the infusion itself took up to about 20 minutes to complete in this study.

We all know the effective half-life of phenylephrine following the IV infusion route is about only 5 minutes; therefore, you will miss a lot of phenylephrine system exposure or AUC values if you only start to collect PK samples at the end of the infusion. This will artificially lower the AUC values following the IV infusion, and consequently artificially inflate the oral bioavailability value. In other words, for a fair and more appropriate comparison, the authors of this paper should collect the first PK sample following the IV infusion starting at minus 20 minutes in this figure.

I'll defer to Dr. Michele.

DR. MICHELE: Thank you, Dr. Ren and Dr. Le. Just to follow up on your question with regard to communication about these results to the public, the first thing that I want to note is that all of the data that we presented today is taken from publicly available sources, so all of these data are available to the public.

The second thing that I want to note is that the point of this meeting is to help us think about what these data show, so you'll note that the final question that's in your briefing document and in the final questions that were submitted to the committee is to talk about the communication of this information and how that might be best communicated to the public, if at all. So I rely on this committee. I know that we have several experts on the committee with expertise in public communication and risk communication, and I'll look forward to a meaningful discussion on that point on day 2. Thank you.

DR. LE: Thank you for that. I'd like to

continue with the clarifying question for Dr. Pham.

DR. COYLE: Go ahead, Dr. Le.

DR. LE: I believe it was slide 116 that was presented where you were providing retail sales, point of sales data, from different pharmacies, et cetera, and one of the exclusions that was listed was Costco. Now, I know the data there could be overwhelming and significantly increase the numbers, but I'm curious as to why Costco was excluded.

DR. MICHELE: I'll turn that question to Dr. Pham.

DR. PHAM: Hi. Tracy Pham, FDA. So we have contracts with outside vendors to get these databases, and Costco is one of the retail stores that would not provide the data to that vendor. So it's just something; that they don't want to publicly share that information. So that's why we don't have sales from Costco and other retail avenues like Amazon or internet sales. We don't get that information either. It's just because it's just not available to the vendors that collect

that data.

Does that answer your question?

DR. LE: Yes. Thank you very much. That's all I have.

DR. COYLE: Thank you. Dr. Le.

Dr. Figg, you you may go ahead.

DR. FIGG: Hi. I'd like to follow up with --

DR. COYLE: Please do state your name for the record.

DR. FIGG: Oh, sure. William Figg from the National Cancer Institute. I would like to go back to Dr. Ren's slide that he just showed in response to Dr. Le's question, the IV versus the oral.

DR. MICHELE: Could we have backup slide number 12, please? And I'll turn the podium to Dr. Ren.

DR. FIGG: So is this the same 10 milligrams for each? Is that correct?

DR. REN: No, it's not. As you see, it's tritium-labeled phenylephrine at that time, conducted in this study, that the dose is not

10 milligram.

DR. FIGG: What is the dose?

DR. REN: As presented on this slide --

DR. FIGG: Oh.

DR. REN: -- it's 0.99 milligram.

DR. FIGG: Okay. Got it. And how does that correlate with the C_{max} with the 10 milligrams then, or the oral?

DR. REN: This is Yunzhao, from FDA. A completely different analytical method was used in that 1982 paper, so I can't do even an orange-to-apple comparison because it's different, very different, a very old-fashioned bioanalytical assay. So here you may notice the absolute value on the Y-axis, it's the log scale, but we can't really compare that absolute value to the nowadays value right now.

DR. FIGG: Yes. I mean, it seems to me -- and I apologize, but it seems to me that there is more to the difference in the bioavailability than simply the sampling time here, but we have to compare those. Because if I

remember the slides you showed previously, you were showing the C_{max} for 10 milligrams to be incomparable to this, and this is 10 times less milligrams being given.

Let me ask one other question. The PK associated with the total phenylephrine is unusual. Most of the time we do not report all the metabolites to come up with PK. Why was that being done by whoever published it?

DR. REN: Okay. Let me go back to history. As I have shown, the phenylephrine concentration, the plasma concentration following the oral dose, is very, very low. It has been challenging in the last century to accurately, reliably measure this parent phenylephrine concentration in the last century, and barely successful. So therefore, that's why different sponsors/investigators, they turn to measure the total phenylephrine concentration, including the phenylephrine, which is hydrolyzed from the metabolites. That's how we come into the PK measurement.

It was not until the turn of this century

that some more sensitive LCMS methodology was developed so that more sponsors and investigators can measure the parent phenylephrine more accurately. And here I said this is a very old-fashioned, probably not even HPLC method. Because it's a very different method, you can't really compare the absolute value from this study to the current studies.

DR. FIGG: Yes. I mean, I've been doing pharmacokinetics for 35 years and have never published where I report the total metabolites plus the parent for pharmacokinetics. It's very unusual, but I thank you for the answer. I thank you so much.

DR. REN: Thank you for the question.

DR. COYLE: Thank you.

I'm looking to see if there are any further questions from the committee.

(No response.)

DR. COYLE: Since we do have some time, I may ask a question of my own. It's Maria Coyle, and this question would be directed to Dr. Starke.

I'm wondering if you could revisit or re-explain a couple of points from the more contemporary trials that you walked us through so expertly earlier. In particular, the dose-ranging trial from Merck, you had discussed how the findings could be interpreted in the context of the study method only being partially blinded. I think it would be helpful for me, and maybe others, to hear that explanation again, if you don't mind.

DR. MICHELE: Could we have slide number 62 up, please, from the main slide deck?

DR. STARKE: Hi. This is Dr. Starke. So it's a little complex to try to describe what happened here because the publication and the results that are at clinicaltrials.gov don't quite mesh. Clinicaltrials.gov describes 5 placebo doses for each -- up to five for each, meaning that it was dummied with placebo along with the active, and patients could see the difference because they were both read, but one had some concave in the tablet, so they looked a little different. That is both the explanation for the partial blinding, and also

there's some confusion in terms of how many tablets each subject got at each time point.

Did I answer your question or do I need to go further?

DR. COYLE: That's very helpful context. You had gone on to provide some additional explanation of how you felt this might potentially have impacted the results, so if you could maybe just restate that for my benefit. Thank you. Maria Coyle.

DR. STARKE: Certainly. This is Dr. Starke again. As you see in the blue boxes, there were 4 doses of phenylephrine given but only 1 dose of placebo. So if patients were to guess their allocation, they would have a 4-to-1 chance of guessing that they were on some dose of phenylephrine. Now, they might be able to or might not, based on the partial blinding, and be able to guess the approximate dose. If you think about patients thinking that they're on an active versus on placebo, it would tend to make it more likely to see a difference between active and control.

Does that answer your question?

DR. COYLE: Yes. Thank you.

I'm going to call on Dr. Calis at this time for an additional question.

DR. CALIS: Thank you. Karim Calis from the NIH. My question is also for Dr. Starke. First of all, thank you very much for an excellent overview. That was really very helpful for me. My question has to do with the study endpoints, and you discussed those, and you've identified some of the limitations, for example, with the the nasal airway resistance and so forth.

If you can maybe elaborate for me -- I don't have expertise in this particular area -- in terms of what is done in contemporary studies, not studies necessarily with these particular agents, just in terms of that particular specialty; and if you can comment maybe on that and why one particular endpoint might be favored over another. I'm looking at objectivity/subjectivity of the outcome measures et cetera, but if you can elaborate more on contemporary studies in this

area.

DR. STARKE: Certainly. This is Dr. Starke. I'm happy to, and I know there's also a panel member who is an expert in this area as well. Actually, there may be more than one, and they may want to chime in as well.

So yes, it is entirely correct, and you can go to slide 97, main slide 97. It's entirely correct that nasal airway resistance is theoretically an objective measure, and it's reasonable to expect, under normal circumstances, that an objective measure might have some meaning. There's a problem, however, with this measure, and I outlined it in the talk, and let me just briefly hit on them.

First, it's not a standardized measure. There are multiple publications that suggest ways to get the results from this NAR measurement, and each of those uses a slightly different technique. As I described in the Columbia study, if you read that publication, you see that they attempted to look at the various techniques that had been

published, and they couldn't come up with one that was able to be repeatable to get demonstratively repeatable results. So what did they do? They actually used a naval diving mask to create their own methodology. So what you have is a non-standardized technique -- that's number one -- and it doesn't necessarily translate from one study center to another.

Number 2, there's no information about how those NAR results, those objective results, which theoretically ought to be reasonable, translate to a clinical benefit in nasal symptoms. There's just no information; we looked. The best you can do is actually that EEU study that Schering-Plough Merck did, and it used pseudoephedrine, which was effective, but phenylephrine was not compared to placebo.

Finally, here you've got a surrogate endpoint instead of actually using the symptoms themselves. All the later studies, all the newer studies, use symptom scores. That has actually been what has been used for the approval of, as far

as I know, all the allergic rhinitis drugs, including all the second generation antihistamines and various other intranasal products, intranasal corticosteroids, intranasal antihistamines, and so on, since the early '90s.

NAR has not been used in drug development for any of these drugs that I am aware of, so we have no correlation between one and the other, and we wouldn't go back and use NAR with that correlation, and you can't use the same studies to validate, has to use, or the results. We don't even have the validation from the original studies because they are entirely opaque in terms of how the symptoms were collected. Thank you.

DR. COYLE: Thank you.

Did that address your question?

DR. CALIS: Yes. Thank you.

DR. COYLE: Excellent.

Maria Coyle here. Dr. Starke, before you step away, could I ask one follow-up question? You mentioned that there is no clinically significant known change in airway resistance, nasal airway

resistance, that would tell you that something is efficacious in relief of symptoms. Is there a change in that nasal congestion symptoms score that we would consider clinically significant, that's accepted as a standard?

DR. STARKE: This is Dr. Starke. I don't have the results for nasal symptoms scores in terms of minimally effective difference for the various drugs that have been approved, but I know that Dr. Dykewicz, one of the panel members, has published many important differences, and perhaps he can help in elucidating the answer.

DR. COYLE: Yes. Dr. Dykewicz, you have the floor. Your hand is also raised.

DR. DYKEWICZ: Yes. I'm responding to the request. Mark Dykewicz. I published in a number of areas, not only minimal clinically important differences but also been co-editor on NASH and rhinitis guidelines, where we've looked at all this type of data, and I guess I would summarize and make a couple points.

We view the patient-reported symptoms scores

as being the real benchmark by which we judge the impact or the effectiveness of medications. Physician or investigator assessed improvements in symptoms has really been set aside, and this is relevant to consideration of the LEGACY studies. We're not really sure what the basis of these symptoms score recording was, how much of that was investigator and how much of that was patient reported.

The other important point is that in terms of nasal airway resistance, that has also been over time reduced in importance in the sense that you don't always get a great correlation between a symptom report of congestion and the so-called objective measures of nasal error resistance. So as we look at the data, I hang my hat on the symptom scores in terms of congestion. Specifically, it could be assessed in the morning. In the evening, you can do reflective symptoms scores over the previous 12 hours, looking over an entire week. There are different ways you can mix and match the data. But these are all ways of

trying to get a sense as to not only shorter term but longer term impact on nasal congestion over a day and over a week, which of course is relevant to our deliberations. That would end my formal comments.

DR. COYLE: Thank you, and that addressed my question as well.

Dr. Dato, I see your hand raised. Please go ahead.

DR. DATO: Hi. Mark Dato. A question to either Dr. Starke, or Dr. Dykewicz I guess now. Can either of you comment on what looks like overall response differences between the different patient populations, specifically allergic rhinitis versus cold, and why you posit those differences? It can be any of the agents, but there seems to be response differences. Thank you.

DR. MICHELE: Hi. This is Terry Michele, Nonprescription Drugs, FDA. Just to make a couple of comments about the differences between the platform of allergic rhinitis and the platform of colds -- and this was mentioned by Dr. Starke in

his presentation -- allergic rhinitis tends to give you a more consistent symptoms score over time because typically during the allergic rhinitis season, as long as the pollen counts are up, people tend to have fairly consistent symptoms scores from day to day; whereas, everyone understands the natural history of a cold is quite variable and tends to be quite short. So enrolling subjects in a study of the common cold can be quite difficult because you can't get those consistent symptoms scores from day to day or even from hour to hour, and it's a very short window, so I'd note that first of all.

The other thing that I would note with regard to the data is that most of the studies that were done in the common cold were the studies that were from the original DESI data set, so those studies had all the methodological limitations that we've just elucidated and gone over in great detail. The one study that was done in the common cold in the newer era, if you want to put it that way, is the J&J study that was stopped early for

lack of enrollment, and that study did show no difference between placebo and phenylephrine, but as I noted, it was stopped early.

So I'll stop there, and thank you for that question. I don't know if other members of the panel wanted to respond to that as well.

DR. DATO: So just real briefly, thank you for that. What I'm hearing, then, is you attribute the differences to methodologic differences, not pathophysiologic differences between AR and cold. Is that a true statement?

DR. MICHELE: Yes. I'd also note that the indication for phenylephrine in the monograph is for nasal congestion, and it does not differentiate between etiologies.

DR. DATO: Okay. Thank you. That's all my questions. Thank you.

DR. COYLE: Thank you, Dr. Dato, and thank you Dr. Michele.

I do not see additional questions waiting, and it is, according to our agenda, now time to break for lunch. So we will go ahead and do that,

and we will plan to reconvene at 12:55 pm Eastern Time. Panel members, just a reminder that there should be no chatting or discussion of the meeting topics with other panel members during this lunch break. Additionally, we would ask that you plan to reconvene around 12:45 pm to ensure that you are connected before we restart the meeting at 12:55. Thank you.

(Whereupon, at 11:56 a.m., a lunch recess was taken, and meeting resumed at 12:56 p.m.)

A F T E R N O O N S E S S I O N

(12:56 p.m.)

DR. COYLE: Welcome back.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including industry's non-employee presenters, to advise the committee of any financial relationships that they may have with industry, such as consulting fees, travel expenses, honoraria, and interest in industry, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning

of your presentation, it will not preclude you from speaking.

We will now proceed with industry presentations.

Industry Presentation - Marcia Howard

DR. HOWARD: Thank you. My name is Marcia Howard. I am a vice president of Regulatory and Scientific Affairs at the Consumer Healthcare Products Association or CHPA. CHPA is one of the oldest trade associations in the country. For more than 140 years, CHPA has worked to ensure Americans have access to safe and effective OTC medicines. These are products that consumers can count on to be reliable, to be accessible, and to save them time and money, and to deliver products to get and stay healthy.

We bring a science-driven perspective to all our work, from regulatory interactions to consumer education. CHPA's membership includes the leading manufacturers and suppliers of consumer healthcare products, including the nine member companies involved in the manufacture and repackaging of OTC

oral phenylephrine medications. These companies comprise the CHPA Phenylephrine Task Group. The logos of the task group member companies are shown on this slide.

We appreciate the opportunity to be part of today's discussion about OTC oral phenylephrine and to review the newer studies of this ingredient. We'll do this in the context of the body of science that established its efficacy. Here you see the phenylephrine drug facts label that illustrates the uses: temporary relief of nasal congestion due to the common cold, hay fever, or other upper respiratory allergies. However, our presentation on monograph studies will focus on the common cold, as most were conducted in that indication.

CHPA member companies currently offer 10-milligram phenylephrine under the marketing authority of a final administrative order. The adult dose is 10 milligrams every 4 hours, not to exceed 60 milligrams in 24 hours. Phenylephrine is a decongestant active ingredient. The category of OTC nasal decongestants includes nose drops and

sprays, eye drops and tablets, capsules and syrup. Not all decongestants, however, are easily accessible to consumers, and consumer preference by 3 to 1 is for oral formulations rather than intranasal.

Phenylephrine and pseudoephedrine are the only oral decongestants available over the counter, however, only phenylephrine is available on shelves without restriction, meaning PE is not restricted to behind the counter like pseudoephedrine. Phenylephrine products occupy a substantial amount of shelf space among cough and cold products and is sold as single-ingredient products or as combination products, which make up 92 percent of sales. Oral phenylephrine has a dosing duration of no more than 7 days. FDA has also identified a few alternative treatments, including intranasal steroids and intranasal and oral antihistamines.

I'd like to briefly review phenylephrine's regulatory status. By way of background, there are two pathways for a medicine to get OTC status and be marketed in the United States. One pathway is

through a specific individual new drug application or NDA. NDAs typically are submitted to FDA with clinical studies to support OTC access for individual products and granted FDA marketing approval. The second pathway, and the pathway relevant for this meeting, is the OTC monograph system. It is a methodical scientific process in which FDA uses expert advisors to systematically and efficiently review the data and literature of hundreds of established ingredients already found in thousands of medications at that time.

Monographs are often referred to as a rule book or recipe for therapeutic categories. They establish the active ingredients, the uses and indications, doses, routes of administration, labeling, and testing requirements that are allowed for a particular category. When FDA's advisors found that there was sufficient data to confirm the safety and effectiveness of an ingredient, that ingredient was included in the relevant monograph as generally recognized as safe and effective or GRAS/GRAE. Products that meet the rules for being

GRAS/GRAE can be marketed without prior FDA approval, and they do not need to submit additional clinical data. This system gives the FDA the framework to regulate most of the OTC medicines American families rely on today.

Oral phenylephrine was first used in the U.S. 85 years ago, before the monograph system was even created. Since then, there have been multiple key expert reviews of oral phenylephrine. Today's 2023 meeting of the Nonprescription Drugs Advisory Committee, or NDAC, will be the third formal review of the data supporting oral phenylephrine's safety and effectiveness by FDA's expert advisors.

FDA's advisory review panel first collectively reviewed clinical data and the literature regarding phenylephrine in 1976. This successful review led to the establishment of its safety and effectiveness and its GRAS/GRAE status. FDA finalized the monograph for nasal decongestant products to include phenylephrine hydrochloride in the mid 1990s and amended it in the mid 2000s. In response to a 2007 citizen petition, FDA held a

second advisory committee review. There was an additional citizen petition and supplement a few years later that was filed by the same petitioners. This NDAC meeting is being convened to discuss oral phenylephrine as GRAS/GRAE. We believe the data support continued GRAS/GRAE status in the monograph.

Phenylephrine has played an important role in consumers' temporary self-treatment of nasal congestion. It is the only available oral nonprescription medicine for nasal congestion that is sold without having to show an ID or to complete a log book. Oral phenylephrine comes in both brand name and store brand versions.

Nasal congestion is one of the most bothersome symptoms associated with colds and upper respiratory allergies and is linked to decreased work productivity and quality of life, and to sleep disturbances. Consumer satisfaction with oral phenylephrine is high. According to household panel data, half of American households rely on phenylephrine, and over two-thirds of these

households chose to repurchase the medicines, on average 4 times over the year, which is a strong indication of satisfaction. These products are available to consumers on grocery, drugstore, and other retail store shelves, as well as being available online. Oral phenylephrine is available in the United States and globally in places like Canada, Australia, and the UK. It has a wide margin of safety.

In response to FDA's notice for this meeting, we wanted to ensure we understood the voice of the 2023 post-pandemic American consumer. CHPA fielded a cross-sectional consumer study to better understand their awareness and attitudes of phenylephrine, and importantly, their experiences with effectiveness. This was an online survey of 1200 adults who reported using oral phenylephrine within the past 12 months. They told us they rely on phenylephrine again and again.

Their reasons; first, they recognize its effectiveness in treating their nasal congestion, and they see physical and personal benefits from

these medicines. We heard this especially among older consumers and those living in rural often underserved communities. They also made it clear that removing oral phenylephrine would create new burdens on them and on the healthcare system.

Let's dig deeper. Eighty-three percent said phenylephrine helps relieve nasal congestion. This benefit is meaningful to consumers. Two-thirds of consumers reported this relief has a positive impact on them, and it helps them get through their day. The need for congestion relief, which 78 percent reported, is clear. Almost 70 percent said that mild to moderate nasal congestion has a negative effect on their daily activities, on sleep, and on their work.

In particular interest, given the FDA's briefing document, we also asked consumers what they would do if oral phenylephrine were no longer available. Forty-two percent would try to obtain pseudoephedrine, which is behind the counter. A large percentage of consumers who would otherwise self-treat their temporary nasal congestion would

unnecessarily burden the healthcare system if they didn't have phenylephrine. This means engaging with a pharmacist, doctor, or other healthcare provider. Thirty-nine percent would make an appointment with a doctor; 26 percent would go to a clinic or an urgent care. In addition, 14 percent would go without treatment.

The voice of the consumer survey underscores how your discussions today could have unintended consequences on millions, including the more than 50 percent of American households that rely on phenylephrine and find it effective for their needs, and on the overall healthcare system.

First, we know that many consumers would turn to pseudoephedrine, however, there are challenges with pseudoephedrine's availability due to the Combat Meth Act. It would take more than 12-to-18 months for manufacturers to increase the amount of pseudoephedrine that they can make due to regulations involving licenses, security requirements, and the Drug Enforcement Administration or DEA quotas. These are all due to

the potential for methamphetamine diversion.

That's on the manufacturing side. To sell pseudoephedrine, a retailer needs to register with the DEA, conduct and certify employee training, and follow strict recordkeeping and reporting requirements on sales. There is also limited shelf space behind the counter, and as a practical matter, this significantly limits the numbers and types of outlets selling pseudoephedrine.

Focusing on the consumer most importantly, pseudoephedrine is available only behind the counter or retail counter. It has daily and monthly purchase limits and requires signing a log book and showing identification. These restrictions pose unequal burdens on consumers who live in areas with limited access to pharmacies based on geography, such as rural areas and other areas in pharmacy deserts, those whose work schedules don't coincide with when pharmacies are open, and those with other socioeconomic factors. As we saw in the survey, many self-care consumers may try to go to a doctor's appointment or to

urgent care, which will mean new and increased resource burdens, or they would go without treatment. This could lead to potential for worsened clinical outcomes.

During our review today, we'll address issues cited by FDA in its briefing materials and misconceptions about phenylephrine. Specifically, we oppose removing oral phenylephrine from the final monograph. Our position is that the totality of the evidence supports the status as generally recognized as safe and effective. Consumer repurchase data indicates high consumer satisfaction, and through the attitude survey, the voice of the consumer reinforces their satisfaction with oral phenylephrine's effectiveness.

We will also address misconceptions about phenylephrine's efficacy as it relates to bioavailability, in vitro potency and clinical PK, and the lack of clinically significant adverse pressor effects at its labeled dose. We'll also address our position on nasal airway resistance. This primary objective endpoint was used in the

monograph studies along with subjective measures. Our position is that NAR remains an appropriate objective endpoint to assess phenylephrine's labeled indication: temporary nasal decongestion.

FDA refers to the monograph studies in its briefing document, but the scientific basis and the measurements of these studies are nonetheless still appropriate and relevant today. We'll also discuss the post-2007 allergic rhinitis studies, which FDA contends do not support efficacy. Certainly, these newer studies have limitations, so we look forward to this committee's thoughts on their interpretability.

We'll also discuss the two meta-analyses presented at the 2007 NDAC. FDA refers to them as inconclusive, however, we'll show that Dr. Kollar's meta-analysis used the more clinically relevant endpoints and methods. Lastly, we will also provide our perspective on the potential for significant unintended consequences of a change in phenylephrine's GRAS/GRAE status. Our position is that this is a safe and effective medicine, and its

removal would result in increased demand for pseudoephedrine and a shortage of FDA-approved on-shelf medications. It would have supply chain implications and would cause an increased burden on the consumers we serve and on the healthcare system.

We appreciate the committee's attention for these discussions today. Here's our agenda for the rest of the presentation and the experts who will speak to these issues. All outside speakers are being compensated for their time. We also have two additional responders with us today. Thank you, and I will now turn the podium over to Dr. Druce.

Industry Presentation - Howard Druce

DR. DRUCE: Thank you, Dr. Howard, and good afternoon. My name is Howard Druce. I am a practicing allergist, immunologist, and clinical professor of medicine at Rutgers New Jersey School of Medicine in Newark, New Jersey. I've specialized in researching and treating conditions such as allergic rhinitis, non-allergic rhinitis, the common cold, and sinusitis for over 30 years.

I am here today because of my clinical and research background in nasal physiology, as well as clinical practice. I have spent most of my career developing clinical endpoints for symptoms such as nasal congestion, cough, and other respiratory symptoms.

Before I address issues regarding the efficacy of phenylephrine, I would like to walk you through the pathogenesis of nasal congestion. It is well known, and it is my clinical experience, that most people who have upper respiratory allergies, whom I will refer to as sufferers, have limited, transient, or mild symptoms, and self-manage their condition appropriately. If they need medication, they can go to a drugstore or supermarket and buy what they need at the time to relieve their symptoms even when the pharmacy is closed. For a common cold, the proportion is even higher. Sufferers rarely need to seek care from a healthcare provider for a cold.

Oral phenylephrine 10 milligrams is fit for purpose in my perspective because it is labeled to

provide temporary relief of nasal congestion caused by the common cold and upper respiratory allergies. As you will see in this presentation, I will demonstrate ample evidence based on appropriate clinical endpoints to justify its specific labeled indications.

Let's consider temporary nasal congestion. How does it occur and what is the pathology behind it? Sufferers who have a common cold or the early symptoms of upper respiratory allergies experience dilatation of the blood vessels in the lining of the nose overlying the turbinate bones. They may also have increased nasal drip.

The inside of the nose is lined with tiny blood vessels, arterioles and venules, which connect to the capillary sinusoid bed. Blood flow is increased to these blood vessels when the nose is irritated, regardless of the trigger. This causes swelling within the nasal lining, blocking the nasal passageways, making breathing difficult. Also, mucus glands within the nose secrete more mucus to trap allergens or other irritants,

contributing to nasal congestion and creating a sensation of stuffiness.

Nasal decongestants act upon sympathomimetic alpha-1 receptors within the nasal mucosa. The alpha-1 receptors are found on blood vessels throughout the body, with large numbers found in the arterioles and venules, supplying blood to the capillary sinusoids inside the nasal turbinates. The turbinate mucosa is the major site of local action for decongestant drugs. The capacitance blood vessels within the mucosa above the turbinates alternate between congestion and decongestion during the nasal cycle.

The degree of swelling of the nasal lining varies throughout the day on a cyclical basis. Usually, we only detect this by noting we are breathing through one nostril or the other. The left plot shows a sufferer's spontaneous changes in unilateral nasal airway resistance over time, perceived as nasal congestion while suffering from an acute respiratory tract infection. This nasal cycle is only perceived as congestion when the

cycle is exaggerated with conditions such as colds and upper respiratory allergies. On the right plot is the same person 6 to 8 weeks later, showing virtually no increased nasal resistance.

Dilatation of the blood vessels within the lining of the inferior turbinates is the major feature of temporary nasal congestion, but also there is increased nasal fluid containing mucus, which together results in the narrowing of nasal passages and the perception of nasal congestion and stuffiness.

The mechanism by which decongestants produce their action is activation of post-junctional alpha adrenergic receptors found on the precapillary and postcapillary blood vessels in the nasal mucosa. Activation of alpha receptors is by either direct binding of the sympathomimetic agent to the receptor's binding site or by the enhanced release of norepinephrine. This results in vasoconstriction. This vasoconstriction decreases blood flow through the nasal mucosa and results in shrinkage of the tissue.

Nasal congestion is the most bothersome symptom of the common cold and upper respiratory allergies. Common cold and seasonal allergic rhinitis are different conditions based on the etiology, pathophysiology, time course, and their different response to medications; however, the mechanism of vasoconstriction is the same in both cases.

In established allergic rhinitis, the inflammatory IgE mediated hypersensitivity response affects the overall tissue recoil of nasal turbinates, and using vasoconstrictors alone may not remediate nasal congestion. Congestion due to the natural cold or due to upper respiratory allergies is an acute condition that is self-diagnosed and self-treatable by the vast majority of consumers using over-the-counter products without healthcare professional consultation.

Let us now look at the histopathology. Common cold and allergic rhinitis have different histopathology, but of note, there are no

differences seen in the blood vessels. In the common cold, we see sloughing of epithelial cells in the nose with completely intact epithelial lining, early neutrophil migration by the second day, and no involvement of mast or other cells. Allergic rhinitis on the other hand includes a thickening of the basement membrane, goblet cells, and squamous metaplasia. An increased number of mast cells, and eosinophilia may be present. Stromal markers also show edema and fibrosis, which characterize remodeling and subsequent turbinate hypertrophy.

Nasal congestion is the most frequently reported and most bothersome symptoms for cold sufferers. Based on symptoms reported by sufferers throughout a cold episode, nasal congestion, in blue, starts on day 1, and is the most frequently reported symptom across the 7 days of a cold. By days 2 through 5, this symptom has become the most bothersome cold symptom. This time course illustrates the importance of using a short-acting decongestant such as phenylephrine in the treatment

of the common cold, whether as monotherapy or in combination.

Most of the phenylephrine used for common cold symptom treatment is found in combination products, which can treat other concurrent nasopharyngeal symptoms. An oral combination product containing a decongestant can provide a more complete and clinically meaningful benefit to the sufferer.

I want to switch now to discussing the use of phenylephrine in upper respiratory allergies. I make an important distinction between sufferers with allergies which last for a few hours or days and patients who have been diagnosed by a healthcare professional as having seasonal allergic rhinitis. The majority of sufferers self-manage their symptoms. Adequate symptom relief is obtained by lifestyle modification such as avoiding allergy triggers, using over-the-counter antihistamines for sneezing, drip, and eye symptoms, and taking over-the-counter decongestants for congestion.

For these sufferers, nasal congestion is typically transient, lasting hours or days, occurring more frequently on peak allergy exposure days. On the other hand, patients who are diagnosed with seasonal allergic rhinitis typically have persistent symptoms for several weeks of an allergy season and may require other treatments. It is important to note that phenylephrine and phenylephrine combination products are not intended to replace other treatment choices in established seasonal allergic rhinitis.

In summary, it is well understood that upper respiratory viral infections such as the common cold and upper respiratory allergies are different conditions with different pathophysiology. When we review the scientific literature, we see no difference in the blood vessels and the mechanism of congestion and decongestion. What is different is that it is more difficult to detect evidence of decongestion in established and persistent seasonal allergic conditions, which we will show, and it is critical that the most appropriate clinical trial

endpoint is chosen to reflect this.

Before I discuss the studies that support the efficacy of phenylephrine, I will pass the presentation to Dr. Gelotte to describe the pharmacology.

Industry Presentation - Cathy Gelotte

DR. GELOTTE: Thank you, Dr. Druce, and good afternoon, everyone. I'm Cathy Gelotte, a clinical pharmacology consultant currently working with CHPA. Previously, I was employed by Johnson & Johnson for 25 years, supporting OTC medicines, but have since retired. During my tenure at J&J, I conducted studies on the pharmacokinetics of phenylephrine following the 2007 NDAC meeting. Today, I will briefly review the clinical pharmacology of phenylephrine, which is consistent with the dosing direction and labeled indications. I'll also address a few misconceptions regarding phenylephrine's bioavailability and potency, with inferences on efficacy.

This figure shows the plasma concentrations

of phenylephrine over 4 hours following an oral dose of 10 milligrams in healthy adults. During absorption, phenylephrine undergoes high first-pass sulfate conjugation in the intestinal wall. When these same concentrations are plotted on the log scale, we see two distinctive slopes. The first is associated with rapid distribution of phenylephrine out of plasma to the sites of action. The second slope reflects the short elimination half-life, about 2 hours, which is consistent with phenylephrine's dosing interval of 4 hours.

The apparent volume of distribution is very high, much higher than total body water, which indicates phenylephrine's preference for tissues outside of plasma and its relatively low bioavailability. The absolute bioavailability of phenylephrine was estimated at 38 percent in one published study using a radiolabeled technique, which has scientific limitations. We are not aware of any new study that uses contemporary assay methods to confirm this estimate.

Next, I'd like to consider the standard

method to estimate absolute bioavailability, and then to address misconceptions that low bioavailability indicates a lack of efficacy. Both absolute and relative bioavailability are determined from concentrations of the same chemical form of the active moiety. The 2015 citizen petition and other briefing materials estimated bioavailability in a different way.

This figure shows pharmacokinetic profiles for a drug assay directly in the plasma compared with total drug, which is the sum of the drug and the drug cleaved from its metabolites. Using the ratio of areas under these two curves, a much lower bioavailability is obtained. For phenylephrine, estimates less than 1 percent were presumed using this method, but this comparison is not valid because the red line for total drug represents the combined pharmacokinetics of the drug and its metabolites. Basic principles are violated when the AUC of total PE is used in the calculations. First, this AUC reflects one or more inactive metabolites, with each having different volumes of

distribution and elimination rates that alter the overall AUC, and concentration data must be corrected for differences in molar masses among chemical moieties.

Although the bioavailability of phenylephrine has not been confirmed, it is noteworthy that even when a drug has low bioavailability, it does not mean a lack of efficacy or minimal efficacy. We know that other factors have a role in determining efficacy such as drug concentrations at the site of action.

Like phenylephrine, many FDA approved medicines have low-to-moderate bioavailability, and several examples are listed in this table. Some drugs, such as bisphosphonates that treat osteoporosis, are less than 1 percent bioavailable; however, the therapeutic effects of medicines with low bioavailability were demonstrated at the oral doses clinically tested. In other words, clinical dosing of a drug accounts for its bioavailability. For phenylephrine, the 10-milligram dose was tested and found to be an effective nasal decongestant in

studies of patients with colds.

Regarding phenylephrine's mechanism of action, we know that it stimulates alpha-1 adrenergic receptors, resulting in vasoconstriction of the nasal mucosa. Phenylephrine's decongestive action stems from the constriction of local arterioles that lead to capillaries, which serve as the major site for fluid passage. Arteriole constriction decreases the amount of fluid entering the densely packed capillary beds of the nose and promotes shrinking of swollen turbinate membranes. The therapeutic outcome is easier breathing due to diminished nasal airway resistance along with decreased stuffiness. Notably, minimal adverse pressure effects are observed at the 10-milligram therapeutic dose because much higher concentrations of phenylephrine are needed for significant constriction of peripheral blood vessels.

In the next few slides, we'll address the misconception that in vitro potency and clinical PK data are not consistent with oral PE being effective. Potency and efficacy are frequently

mixed up, but these terms are not synonymous. Potency is the concentration of drug needed to produce a certain response. It depends on the rates of receptor binding and release and receptor affinity, among other factors. Efficacy is the ability of a drug to elicit physiological responses when interacting with receptors. It has more complex dependencies, but intrinsically relies on the number of receptors. Stimulation of these receptors may be expressed differently among tissues, leading to different responses.

Potency is just one contributory factor of clinical efficacy. Supplements to the 2015 citizen petition and today's briefing materials provide examples of in vitro potency data for phenylephrine, such as the EC_{50} shown here. They are generally higher than clinical plasma concentrations, but this does not mean phenylephrine lacks efficacy.

Many drugs have clinically effective concentrations that are lower than estimates in in vitro potency. In a published analysis of

164 registered drugs, the ratio of the effect of plasma concentrations at steady state to in vitro potency was estimated for each drug. This figure shows the cumulative frequencies of these ratios, sorted by the type of potency measured, including the EC_{50}. About 70 percent of the ratios were at or below unity with a median ratio of 0.32.

Data for a few allergic rhinitis drugs from this analysis are summarized in this table and compared with data for phenylephrine. I'd like to point out that the measured clinical concentrations include drug both unbound and bound to plasma proteins, but it's the free unbound drug that distributes to tissues and interacts with receptors, resulting in efficacy.

The speculation that orally administered phenylephrine cannot achieve effective concentrations based on in vitro potency data is without merit. The plasma concentrations of phenylephrine measured over 4 hours are consistent with 10-milligram phenylephrine being effective because the time course and intensity of effects

depend on drug concentrations at the site of action.

To illustrate the pharmacodynamic relationship with measured concentrations, we overlay data on nasal airway resistance, a measure of nasal congestion, from a subset of clinical studies from the monograph review. Note that data for the percent reduction in resistance is inverted on the right axis for an easier comparison with the plasma data. We see a slower onset, where the response curves are shifted to later times compared with the time course for phenylephrine concentrations.

In addition, the overall duration of effect diminishes by 4 hours, which aligns with phenylephrine's labeled dosing indication and indication of temporary relief. These data show that the nasal vasculature is responsive to concentrations associated with the 10-milligram dose.

Another way to look at the pharmacokinetic and pharmacodynamic relationship is to plot the

phenylephrine plasma concentrations and NAR response data at each common time point. This display provides insights into the complexity of drug action and its disposition. For phenylephrine, we see a counterclockwise hysteresis loop. This loop means that there is no direct relationship in time with the concentration; rather, we see NAR responses increasing over time, even after drug concentrations have begun declining. In other words, there continues to be measurable NAR effects at later times following the 10-milligram dose, even though measured plasma concentrations are approaching zero in a pharmacokinetic curve. Possible mechanisms for time delay in phenylephrine's response includes delayed distribution kinetics and uptake into active tissue sites.

Next, we'll address the misconception that the lack of significant adverse pressure effects in the recent pharmacokinetic studies supports the lack of decongestant efficacy. Although direct stimulation of the nasal and peripheral vasculature

with phenylephrine results in vasoconstriction, the available science suggests that the overall clinical responsiveness varies between tissues. Reasons for differential decongestion and hemodynamic responses include potential differences in distribution and density of adrenergic receptors and differences at concentrations at effect sites; however, the most important difference is the body's homeostatic response to increases in blood pressure where baroreceptors are stimulated. This results in a decrease in heart rate, which diminishes the pressure response.

Let me walk you through an example of diminished pressure responses using data from a recent pharmacokinetic study. The pharmacokinetic profile for 3 doses of phenylephrine in 28 adults are displayed in this figure. The study also included the placebo because both blood pressure and heart rate were measured at several times over 4 hours.

Mean changes from baseline for these hemodynamic effects are plotted for each dose and

for placebo. We see that the time action curves for blood pressure and heart rate are mirror images of each other. With phenylephrine vasoconstriction, blood pressure increases. This stimulates baroreceptors that respond by decreasing heart rate, which then diminishes further blood pressure responses. Homeostasis is the main reason why clinically adverse increases in blood pressure are not observed at the 10-to-30-milligram doses, but yet, decreases in nasal airway resistance and congestion are observed in the monograph studies.

Let's turn our attention to the range of phenylephrine doses where pressure effects are significant. Having minimal pressure effects in the recent pharmacokinetic studies reinforces phenylephrine's favorable safety profile. At the 10-milligram dose, we would expect to see small changes in blood pressure.

One published study by Martinsson evaluated the relationship between phenylephrine plasma concentration and pressure effects. Increases in blood pressure were evaluated with infused doses of

phenylephrine that attained extremely high plasma concentrations, up to 50,000 picograms per mL. When the range of peak plasma concentrations from the 30-milligram oral dose is highlighted on the figure, we see that clinically important increases in blood pressure are unlikely. We know that oral doses from 50-to-100 milligrams of phenylephrine are needed to attain concentrations high enough to adversely increase blood pressure.

In summary, the concentration profile of phenylephrine shows a rapid distribution to the site of action and supports the labeled 4-hour dosing interval. Importantly, having low bioavailability does not mean lack of efficacy because clinical concentrations consistent with the PE or 10-milligram dose are effective. Specifically, therapeutic effects as measured by NAR were demonstrated in clinical studies at the doses evaluated. Finally, not having adverse pressure effects does not mean lack of efficacy because the baroreflex response to phenylephrine diminishes increases in blood pressure.

Thank you, and I'd like to pass the presentation back to Dr. Druce.

Industry Presentation - Howard Druce

DR. DRUCE: Thank you, Dr. Gelotte.

I will first discuss methodology, and then present data from some of the several monographed clinical studies that demonstrate the efficacy of oral phenylephrine. Most of the monographed clinical studies used a natural common cold model with an objective endpoint of measuring nasal airway resistance. This was for a very good reason. The short-term effects on the blood vessels are similar in both the common cold and upper respiratory allergies, and extrapolation from the common cold model is valid.

I want to stress up front that both objective and subjective measurements provide valuable data; however, a primary objective endpoint is critical to capture short-term decongestant changes typical of drugs like phenylephrine. Nasal airway resistance, or NAR, is an objective measurement of nasal congestion and is

the clinical endpoint most appropriate to assess temporary decongestion of over-the-counter phenylephrine as approved in the drug facts label. Subjective measurements of nasal congestion such as reflective scoring of symptoms will be lost in a 12-hour or 24-hour reflective score, especially a 12-hour morning reflective score. Please remember that the dosing interval for oral phenylephrine 10 milligrams is up to 4 hours to provide temporary relief of congestion.

An objective measurement of nasal congestion can be made with multiple techniques, including anterior, posterior, acoustic rhinometry, and peak nasal inspiratory flow. Anterior rhinomanometry has been the most widely used technology for clinical trials because it can measure flow through each nostril separately and is also the method recommended by the International Committee on Standardization of Rhinomanometry. Although this technique is operator dependent, rhinometry is accurate and standardized for small studies.

As mentioned in FDA's briefing materials,

there have been no recent submissions using an objective endpoint as the primary endpoint; however, it is an important endpoint for the clinical trials you have seen. It remains the useful technique to measure changes in nasal congestion and to provide additional insights together with appropriate subjective measures.

With that background, let's discuss the misconception that monographed studies do not support the GRAS/GRAE status of oral phenylephrine 10 milligrams. I'll start by discussing the limitations in study methodology.

Nasal congestion is not only the most bothersome symptom to experience, as I have mentioned earlier, but it is also the toughest to treat and measure. Both the study design and the clinical trial population impact study results. The severity of nasal congestion can be assessed with objective or subjective measurements. The objective measurement that is the most relevant is nasal airway resistance measured with a rhinomanometer, as I have just presented.

Subjective measurements are assessed with a diary and include symptoms scores based on verbal descriptors or a visual analog scale.

Studies performed with different methodologies are difficult to compare. Studies performed and completed after 2007 include randomized, controlled, parallel group studies; allergen chamber studies; and open-label studies, but are all in an allergic rhinitis clinical model. Patient selection in these studies tended to enroll patients with greater symptom severity than typically self-managed temporary nasal congestion.

As you have heard from Dr. Howard, the efficacy of 10-milligrams phenylephrine was accepted in 1976 by FDA review and reaffirmed by the NDAC in 2007. Let's review the data. The 2007 review included 14 studies that evaluated oral phenylephrine 10 milligrams. Seven showed a statistically significant effect on nasal airway resistance, and five of these studies also demonstrated a significant effect based on subjective endpoints. Later in the presentation,

we will discuss some of the negative studies.

The totality of evidence meets the regulatory standard needed to demonstrate efficacy for the labeled indications of phenylephrine. Shown here is a forest plot of the results from studies that evaluated 10-milligrams phenylephrine versus placebo. Nearly all studies were in the common cold model. All compared oral phenylephrine 10 milligrams to placebo and evaluated the reduction in nasal airway resistance over a span of 120 minutes. The light blue shading highlights those that favored phenylephrine 10 milligrams, with six being statistically significant. One study that did show effectiveness is not shown here, as it was not placebo controlled.

I will provide further information on the efficacy of phenylephrine using the results from three representative studies that utilize technology that met the regulatory standard, Elizabeth number 2, Cintest number 1, and Cohen 75.

Elizabeth number 2 was a placebo-controlled, crossover design study that measured nasal airway

resistance and one of multiple studies to demonstrate the effectiveness of phenylephrine 10 milligrams. The gray line represents the placebo and the dark blue line represents phenylephrine 10 milligrams. There was a statistically significant improvement in nasal airway resistance compared to placebo within 15 minutes, which was sustained for at least 2 hours. Cintest number 1 also demonstrated statistical significance of 10 milligrams oral phenylephrine compared to placebo as early as 30 minutes after dosing. This efficacy was sustained for up to 4 hours.

Cohen 75 was a large randomized, double-blind, placebo-controlled study to evaluate the effectiveness of phenylephrine 10-milligram tablets for the common cold. Among the 200 volunteers aged 18 and over, this study demonstrated efficacy soon after taking phenylephrine 10 milligrams as shown by objective measurement of nasal airway resistance. The objective nasal airway resistance measurements are plotted here and show nasal airway

resistance statistically significantly decreased with phenylephrine compared to placebo after 2 hours with an early separation. The efficacy of phenylephrine 10 milligrams was sustained for up to 12 hours with repeat dosing compared to placebo when dosing according to labeling.

The subjective endpoints in this study are also informative and correlated well with the primary objective endpoint. Within 30 minutes, patients achieved a statistically significant benefit with phenylephrine 10 milligrams compared to placebo and was repeated in the dosing intervals thereafter.

FDA and the panel reviewed this study for the 2007 advisory committee meeting. In their briefing book for this meeting, FDA stated that this was a large study, and because of the way the study was described in the Advance Notice of Proposed Rulemaking, or ANPR, pushed the panel in favor of a positive recommendation for oral phenylephrine. We agree with the assessment of the panel and see the position today as unchanged as

evidence supporting the efficacy of oral phenylephrine 10 milligrams in the common cold.

The largest study showed substantial evidence in subjective measures for phenylephrine 10 milligrams that are significant at all time points past 15 minutes, which are clinically meaningful. FDA mentioned in their briefing materials that assessment of clinical relevance was not completed and questioned the clinical value of the study. I'd like to share the results of a recently completed reassessment by a statistician from a member company of CHPA that answers this question.

The analysis is based on the raw data obtained from the final study report re-entered and analyzed. The table shows three different accepted methods of assessing clinical significance based on statistical models from Norman et al. and Barnes et al. The green shading highlights the time points at which a clinically meaningful difference was demonstrated. Both statistical significance and clinical meaningfulness are clear from the

study regardless of whether the anchor based or distribution based method is used to assess the minimally important difference.

I'd like to turn to the post-2007 studies and address the misconception that these latest studies negate the efficacy of phenylephrine established previously. Since 2007, there have been attempts to reevaluate the efficacy of phenylephrine, albeit with different methodology. Four clinical studies all in seasonal allergic rhinitis were published. The first two were conducted in an environmental allergy chamber and the second two were outpatient clinical studies.

The phase 2 proof-of-concept study by Johnson & Johnson will be addressed separately, as it was posted on clinicaltrials.gov, but we note that the study was an incomplete study terminated early due to the inability to recruit the planned number of subjects; therefore, the results should not be considered definitive either way. These later clinical studies do not invalidate efficacy already demonstrated in patients experiencing nasal

congestion due to the common cold.

Not one methodology specifically addresses the labeled indication of oral phenylephrine 10 milligrams intended for temporary relief of congestion. My key issue with these methods is the chosen clinical methods. The design of these new clinical studies is not relevant to evaluating short-acting oral decongestants. Following a thorough review, we identified some important limitations that are listed in this table. They include inadequate blinding; concomitant use of an antihistamine; 12 hours subjective reflective endpoints inappropriately used as the primary; and in addition, enrollment of inappropriate study subjects.

There are also some limitations associated with the earlier clinical studies reviewed by the 1976 over-the-counter expert panel, and they are noted in our briefing book. In the next series of slides, I'll describe these limitations and share our concerns, beginning with the selection of the study populations.

Subjects in these studies do not represent individuals who have intermittent nasal congestion in seasonal allergic rhinitis and manage their own care with the use of over-the-counter medicines, including phenylephrine, for the temporary relief of nasal congestion. This table highlights the main selection criteria from each study regarding seasonal allergic rhinitis.

We see that enrolled subjects had at least moderate severity of nasal congestion per the FDA guidance, except subjects in the Meltzer 2016 study who had at least mild severity. They needed to be symptomatic within two years of the study and have a positive skin test or in vitro test for specific IgE.

We note that in seasonal allergic rhinitis, when people seek medical care due to persistent symptoms, the pathology in their nose is inflammation. This often requires the use of intranasal corticosteroids. Based on the criteria in the last three rows, subjects with more severe and persistent rhinitis were permitted to enroll.

Also, having allergic rhinitis over a long duration of years is a risk factor for the onset of asthma.

Another consideration which may affect the efficacy endpoints is that patients with persistent allergic rhinitis may be less responsive to alpha adrenergic decongestants like phenylephrine. In this published study, the relationship between the duration of rhinitis in years and nasal air flow measured by rhinomanometry was determined in 312 adults. Topical application of naphazoline, a selective alpha-1/alpha-2 adrenergic agonist, was used as a decongestant test. The results are shown in the figure, where we see a strong inverse correlation between improvement in nasal airflow after treatment and the duration of rhinitis.

A review of study populations described in published clinical trials of antihistamines found that the mean rhinitis duration ranged from 12-to-20 years. These data corroborate our assertion that the study populations in the four new allergy studies were not appropriate to evaluate the temporary decongestant effect of oral

phenylephrine.

Let's take a closer look at each study. We also know that adequate blinding of treatments is critical when the primary endpoint is the subjective assessment of symptoms. This is especially true in a crossover design like the Horak 2009 study, where each study receives each treatment sequentially; however, this study was single blind for the investigator only, so the color and shape of the products were visible to the study participants. Commercial products were used for the red pseudoephedrine tablet and the yellow phenylephrine capsule. Some subjects may have been familiar with their respective dosage form and color.

This figure shows decreases in mean congestion scores over 6 hours, with the greatest decrease observed for pseudoephedrine. The authors noted these results may be biased due to subject recall of pseudoephedrine's efficacy from a previous treatment period. In addition, this strongly suggests carryover effects that would

negatively affect the outcomes for phenylephrine.

When efficacy was evaluated by the blinded investigator using objective rhinometry, decongestion was demonstrated for both pseudoephedrine and phenylephrine. Both time action curves overlapped, showing a clear separation from placebo, although differences did not reach statistical significance for phenylephrine; however, dosing 10 milligrams phenylephrine at the 4-hour time point per its labeling would have been more appropriate for evaluating efficacy up to the 6-hour endpoint.

Let's turn to the Meltzer 2015 study. Although this study was based on FDA's draft guidance for new products for allergic rhinitis, every patient was dosed with an antihistamine, loratadine, a variable complicating the evaluation of phenylephrine. This was an open-label study implying that blinding for the study was insufficient for subjective endpoints of symptoms as the primary endpoint. Regarding the study population, subjects had persistent nasal

congestion. We know that in seasonal allergic rhinitis, when patients seek medical care, the pathology in their noses is inflammation, so it is unsurprising that this resulted in a negative study.

Let's look at two limitations in more detail. The first is the daily use of loratadine while 4 doses of phenylephrine were evaluated. Our concern is that loratadine, an antihistamine, provides a halo effect such that the subjects reduced perception of the severity of other rhinitis symptoms biases the scoring of nasal congestion. Let me walk you through an example.

In this published study of seasonal allergic rhinitis, nasal congestion was evaluated after treatment with loratadine alone, a combination tablet of pseudoephedrine with loratadine, and placebo. The mean improvement in congestion for the combination tablet over 4 days was superior to both loratadine and placebo, but after 14 days, the combination tablet with pseudoephedrine was not superior to loratadine alone. We see that relief

from allergy symptoms with loratadine over this longer duration provided a halo effect, which improved the congestion scores; therefore, the overall sensitivity of the clinical model to detect differences among treatments is decreased.

A major limitation of the Meltzer 2015 study is that the phenylephrine doses were not compared with placebo, but rather with loratadine, like this example. The primary endpoint in Meltzer 2015 doesn't make sense for phenylephrine, a short-acting decongestant, because it relies on reflection of changes in congestion severity over the previous 12 hours. This endpoint was developed to evaluate once or twice daily treatments for seasonal allergies, whereas oral phenylephrine is dosed around the clock every 4 hours for temporary relief.

In the Meltzer 2015 study, dosing compliance was low, especially overnight due to the high frequency of dosing. On average, patients took 4.5 doses, which is about 4-to-5 doses out of the 6 doses a day. Taking fewer doses overnight

provides less benefit over the previous 12 hours, thus negatively biasing the morning scores. This is not an appropriate endpoint for evaluating temporary symptom relief.

This next study by Meltzer and colleagues evaluated an experimental modified-release phenylephrine tablet. Two study elements diminished the sensitivity of the clinical model to detect efficacy versus placebo. The first was the daily use of loratadine as needed for allergy symptom relief. Mean exposure for both treatments was about four out of the seven days. Most placebo-controlled clinical trials of oral antihistamines, with and without a decongestant, do not permit as-needed treatment with rescue medication.

The second was the inclusion of subjects with documented seasonal allergic rhinitis for at least two seasons, who reported nasal congestion scores of mild. This grade of severity does not meet FDA's guidance for moderate severity. We see that there is no score between none and mild that

would allow for improvements in congestion severity. Improvement would require a complete resolution, and without an active control, these changes in the model cannot be interpreted.

The final study that I'd like to review is a phase 2 study that investigated an experimental extended-release, 30-milligram phenylephrine tablet in the common cold. This was a placebo-controlled, noninferiority study of extended-release phenylephrine 30 milligrams evaluated over 12 hours and dosed twice, compared with 4 total doses of phenylephrine 12 milligrams taken every 4 hours. Patients were required to have common cold symptoms for up to 72 hours prior to entry.

The study included various subjective endpoints, including some that were exploratory. The study was characterized as proof of concept. It was terminated early due to the inability to recruit the planned number of subjects, even after relaxing an inclusion criterion. Inferences may be made from incomplete data, which should not be considered definitive.

In summary, oral phenylephrine 10 milligrams provides temporary relief of congestion due to the common cold and upper respiratory allergies, which is the labeled indication. There is ample clinical evidence, based mostly on the common cold model, to justify the labeled indication, with FDA determining regulatory status as GRAS/GRAE based on what I consider an appropriate clinical endpoint. The monographed studies are methodologically sound and are still relevant to support GRAS/GRAE status.

No compelling data have been presented to date to challenge this existing efficacy data because the subjective 12-hour reflective symptoms score in established seasonal allergic rhinitis patients does not have the capability to detect short-term efficacy. No novel technology or clinical trial design has emerged to negate the established data or warrant reinvestigation of phenylephrine for its labeled indication.

FDA has reanalyzed the pre-2007 data based on deficiencies in selected trial endpoints. We ask the NDAC and FDA to consider the post-2007

studies from a similar perspective. Thank you. I will now turn the presentation to Mr. Mullin to discuss the meta-analysis.

Industry Presentation - Chris Mullin

MR. MULLIN: Good afternoon. My name is Chris Mullin. I'm a biostatistician with NAMSA, a contract lab and research organization. I'd like to briefly summarize meta-analyses of phenylephrine that were reviewed by this committee in 2007, those by Hatton and by Kollar, touch on some of the criticisms subsequently raised after the 2007 meeting, and explain why these criticisms do not alter the original conclusion of effectiveness of Kollar.

I will show that the difference in the stated conclusions by the authors is not surprising and that it can be attributed to methodologic differences. I will also briefly touch on the newer studies conducted since 2007 and attempt to provide some additional context for these studies.

First, let's discuss the 2007 meta-analysis by the petitioners, Drs. Hatton and Hendeles. This

was based on a literature search of randomized, placebo-controlled trials of oral phenylephrine at 10 milligrams as a single agent. Studies using multiple agents or against the non-placebo control were excluded. This included seven crossover studies and one parallel group study. The endpoint chosen for analysis was the maximum reduction in nasal airway resistance whenever it occurred within the first 120 minutes. This endpoint was identified as problematic by FDA in 2007 since it potentially obscured the differences at time points.

This meta-analysis employed a random effects model and used aggregate summary data from each study. The meta-analysis concluded there was insufficient evidence that oral phenylephrine is effective; however, it actually reported a point estimate of approximately 10 percent for the difference in percent NAR decrease in favor of phenylephrine.

The second meta-analysis conducted in 2007 was by Kollar. This analysis used essentially the

same seven set of randomized-controlled crossover studies as Hatton. Of note, their publication also included an assessment and reanalysis of the parallel group study by Cohen that was included in the meta-analysis by Hatton. The chosen endpoint was assessed at specific available time points through 240 minutes.

Note that the presentation of results at the available time points, whether or not those results were significant, mitigates the concern regarding multiplicity. In other words, the Kollar analysis did not simply pull out and present only the significant results; they also provided non-significant results for disclosure and context.

Another very important difference was that the Kollar analysis was based on individual patient data. It was not based on combining summary measures from previous publications. The approach using individual patient data had advantages. For example, it allowed adjusting for the baseline value for each subject as a covariate. It is well known that adjusting for baseline measurement when

assessing an outcome based on change can increase statistical power. The conclusion of the Kollar meta-analysis was that oral phenylephrine is effective.

On this slide, on the left we see the estimated treatment effect from Hatton, as noted in the FDA briefing book. The analysis shows a point estimate of approximately 10 percent that favors phenylephrine. We see very similar results in the Kollar paper at 60 or 90 minutes as seen on the right, again approximately a 10 percent difference in favor of phenylephrine, so despite all the potential statistical complexities, the results are relatively consistent.

The conclusion of Kollar was based both on the results of the meta-analysis and reanalysis of the individual studies, and on reanalysis of the crossover study of Cohen. This represents multiple sources of data supporting the conclusions. When we focus on just the crossover studies for a moment in this forest plot, we note that three studies appear to individually show an effect and four

studies do not.

I'll discuss study-specific issues of the positive studies in some detail, but first, it is important to point out that several of the negative studies have a clear issue that calls into question their individual conclusions. One study included a positive control but failed to show a significant benefit of the positive control over placebo, and two other studies did not include a positive control group at all. In other words, the three of the four negative studies did not demonstrate assay sensitivity. Accordingly, including these studies in any meta-analysis can arguably bias things towards the null, so in this sense, the Kollar meta-analysis provides a conservative estimate of benefit.

Finally, I'd like to discuss concerns that were raised regarding some of the studies included in the meta-analyses. One concern was based on post hoc analyses that showed the distribution of the last significant digit in baseline values for one study appears to have a disproportionate

occurrence of the number 5 beyond what would be expected by chance. The authors argued this was potential evidence of irregularities, but there are simpler explanations for this finding.

First, for context, these criticisms came more than 40 years after the study was performed and two years after the advisory committee meeting. It's not clear how many post hoc exploratory analyses were performed to identify this issue; and second, the issue of digit preference has been previously reported in the scientific literature in other areas, in studies of blood pressure for example, and it does not necessarily mean there are issues with the underlying data. It may be simple human psychology and rounding error. Additionally, non-random digit preference in baseline values for a blind and randomized trial would not be expected to introduce bias.

The other criticisms related to specific studies were that the data from some of the small studies is suspicious because they exhibit superior efficacy estimates. FDA's briefing document notes

particular questions about the small variability at the Elizabeth labs. Their table is reproduced here, but note this table is derived from an earlier study report by Huntingdon. First, the results for PPA 50 milligram come from a separate study not used in the meta-analysis.

Also, FDA makes no mention of the extremely large standard deviations reported at the Huntingdon lab, with values of 79 and 166 and 180 and 240 minutes, values 3-to-4 times larger than those at either Cintest or Huntingdon for any other study formulation. This suggests potential issues with the results from this lab, a lab that produced negative results in the studies included in the meta-analysis in terms of poor potential conduct.

Considering for a moment the concerns about the significant findings at the Elizabeth lab studies, there are certainly other potential explanations for the results of the studies in question. Borenstein, Hedges, Higgins, and Rothstein discussed the general issue in their introductory textbook on meta-analyses, referring

to the concept of a small study effect. They note that it may be the case that the effect size is truly larger in a smaller study, as a smaller study may involve more highly skilled investigators.

Authors from one of the negative studies in the meta-analysis in fact noted insufficient training and the use of different technicians pre- and post-dosing as possible reasons for their lack of a positive study. More generally, concerns about bias should be symmetric, and so small studies cannot be said to inappropriately bias the mean effect upward any more than the large studies can be said to inappropriately bias the mean effect downward. While we agree the variability is a concern with all studies in this area, this is precisely why conducting studies in this area is so challenging.

It is important to critically review the newer studies to a similar degree as the monographed studies. I'd like to start with the J&J study that was performed after 2007. The J&J study discussed by FDA in their briefing materials

does have limitations that suggest treating the results with care. This cannot be considered a negative study. It does not demonstrate phenylephrine is ineffective. The study was not powered or designed for direct comparisons of phenylephrine to placebo. While it was larger than the monographed crossover studies, it was designed as a parallel group study, which may be less efficient and require a larger sample size than a crossover study.

Also worth noting is that this study was less than two-thirds of the sample size per treatment of the largest cold study, the Whitehall lab study that Dr. Druce discussed. In FDA's materials, they noted the study initially appears to have been designed as a phase 3 study to support approval of phenylephrine; however, the protocol directly states this study was designed as a phase 2 proof-of-concept study. Additionally, as FDA noted in their briefing materials, it lacked a positive non-phenylephrine control group, which could be used to assess assay sensitivity. Also,

the study was terminated early due to the inability to recruit the planned number of subjects. Regardless of the reason for stopping, the smaller sample size reduces the power for any subsequent analysis.

Despite all these limitations, there's still value in examining the results from clinicaltrials.gov. These were also reproduced in the FDA briefing document. And just a note, regarding FDA's slide 71 from this morning, please note that a positive value for mean change does correspond to an improvement from baseline.

The results here are actually consistent with the benefit of phenylephrine. While the primary endpoint was based on a subjective severity score, one can note that both doses of phenylephrine show point estimates in favor of the drug compared to placebo. Further, while the lower confidence bound for the difference from placebo for phenylephrine falls below zero, the upper confidence bound is 0.662, showing that we can't rule out a treatment effect this large. So rather

than this study supporting the conclusion that 10-milligram phenylephrine is ineffective, its results do not contradict the monographed studies. Additional information on this study was submitted to the docket.

A few additional studies of oral phenylephrine have been performed, as Dr. Druce discussed, but for various clinical reasons they're not appropriate for inclusion in meta-analysis. Horak used the Vienna Challenge Chamber in study subjects with seasonal allergic rhinitis and had carryover bias that may have altered results. Dan Meltzer's 2016 studies looked at different formulations of phenylephrine, a quick dissolving strip and a modified-release formulation, respectively, while Meltzer in 2015 used phenylephrine in combination with loratadine, so the potential for confounding is too great. These substantial differences would create interpretation challenges if the studies were incorporated into meta-analyses. Furthermore, Dr. Druce previously stated that common cold and seasonal allergic

rhinitis are different conditions with different responses to medications.

Overall, criticisms of the meta-analysis and new studies do not change my confidence in the effectiveness of oral phenylephrine. To reiterate and conclude, both the Kollar and Hatton meta-analyses included similar studies and produced similar estimates, and superficial differences regarding statistical conclusions can be explained by methodology differences.

While several small crossover studies from the monograph do show significant results, the size of the effects themselves and the small degree of variability may simply demonstrate well-conducted, highly-controlled studies. Several of the so-called negative studies are not free from limitations, specifically a lack of demonstration of assay sensitivity.

Finally, the new studies are also not without flaws. They do not address the current labeling for 10-milligram phenylephrine and the indication for relieving nasal congestion due to

the common cold, and the results do not contradict the monographed studies. Thank you. I will return the presentation to Dr. Howard.

Industry Presentation - Marcia Howard

DR. HOWARD: Thank you, Mr. Mullin, and thank you to this committee for your attention this afternoon. To close this presentation, I'd like to take a few moments to provide our assessment of the overall benefit-risk profile of OTC oral phenylephrine and summarize the CHPA task group's perspective on the key issues.

The CHPA task group on phenylephrine remains convinced of the favorable benefit-risk profile of oral phenylephrine for the temporary treatment of nasal congestion. As we all know, this is a common symptom that is bothersome. It disturbs our sleep, leads to decreased productivity, and can affect our mood. When considering benefits, it is clear oral phenylephrine has a broad consumer satisfaction. Half of the American households purchased oral phenylephrine products for nasal congestion last year, and these phenylephrine buyers, over

two-thirds, chose to repurchase the product again and again. This is a strong indication of consumer satisfaction. This high level of consumer satisfaction aligns with our scientific data review.

The efficacy of oral phenylephrine has been supported by two FDA advisory expert panels. It was established by seven monograph studies and reconfirmed by the Kollar meta-analysis that Mr. Mullin explained earlier. Another important factor is the convenient availability of this oral medication on retail shelves and online, and consumers prefer oral formulations over other types of medications. This is in stark contrast to the potential risk of consumers if they faced a phenylephrine market where phenylephrine was removed. This would leave only pseudoephedrine on the OTC market for oral treatment of nasal congestion.

One of the main concerns with this possibility is that pseudoephedrine is only available behind retail counters and is subject to

other sales restrictions and quotas by the DEA. Quite simply, in terms of access, pseudoephedrine could not meet the needs of consumers, especially for those in underserved communities. As noted in the agency's background materials, no safety issues with orally administered phenylephrine products have been identified.

Phenylephrine's overall safety profile remains favorable. Let me say that again. Phenylephrine's overall safety profile remains favorable. Due to many of these unintended potential risks, some consumers might not be able to choose medication or might choose to leave their symptoms untreated. This could lead to worsened outcomes like sinus infections or sinusitis.

The bottom line is that oral phenylephrine is safe and that it works. Multiple clinical studies using subjective and objective endpoints support its efficacy at 10 milligrams. Multiple consumer surveys also highlight how Americans recognize the physical and personal benefits of oral PE and would be significantly burdened if this

effective medicine were not available OTC. The totality of the evidence satisfies FDA's criteria for inclusion in the OTC monograph. Phenylephrine should remain in the OTC monograph, and it should remain conveniently available to consumers who need it and who already rely on it.

Throughout this meeting, various speakers will offer various interpretations of the data. There are a few fundamental points I'd like you to keep in mind as you consider this information. First, there are clinical data with both objective and subjective endpoints that support the efficacy of oral phenylephrine at the 10-milligram dose. The monograph studies used to establish GRAS/GRAE status meet the regulatory standards for inclusion in the OTC monograph that justify the labeled indication of temporary relief of nasal congestion.

Not every study was positive, but no one would expect every study to be positive when studying nasal congestion due to colds and upper respiratory allergies, and of note, there are no safety signals associated with OTC phenylephrine.

Second, there is no scientific rationale, no new clinical trial design, or no new innovation that negates or invalidates the body of science and established data in the monograph. As discussed in our presentation, the post-2000 studies discussed today have limitations, and therefore should not be used to inform decisions about the GRAS/GRAE status for phenylephrine. Third, as Dr. Gelotte explained, it is critical to understand that phenylephrine's low bioavailability and lack of significant adverse pressor effects do not mean phenylephrine has minimal efficacy. Statements to the contrary are wrong.

Fourth, we also discussed both 2007 meta-analyses and showed how the Kollar meta-analysis utilizes more clinically relevant endpoints and will accept the statistical methods. Its assessment supports efficacy for phenylephrine at the 10-milligram dose. And lastly, there could be significant negative unintended consequences of removing phenylephrine from the monograph for consumers and to the healthcare system. It could

add to the burden of the 50 percent of consumers who rely on this ingredient and those consumers who have told us that they know it helps relieve their bothersome congestion. Thank you, and we'll be happy to answer your questions.

Clarifying Questions

DR. COYLE: Thank you.

We will now move to clarifying questions for the presenters from the Consumer Healthcare Products Association, who we've been referring to as CHPA going forward. Please do use the raise-hand icon to indicate that you have a question. Remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When acknowledged, please do remember to state your name for the record before you speak and to direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the

end of your follow up question with, "That is all for my questions," so that we can move on to the next panel member.

Dr. Le, please go ahead.

DR. LE: Hi there. Jennifer Le from University of California San Diego and the Skaggs School of Pharmacy. I do have questions for each of the presenters. I'll start first with Dr. Howard. I'm trying to ascertain the significance of the consumer's perspective using the survey that you've presented here. Now, on slide 10, if we can go to slide 10 --

DR. HOWARD: Okay. May we share our screen? Thank you.

DR. LE: -- on this slide, as well as the next slide, slide 11, did your consumer survey specifically pertain to only oral formulation of phenylephrine or did it also include the nasal?

DR. HOWARD: We only ask about oral phenylephrine, but I'd also like Mr. Tringale to come and provide additional context.

MR. TRINGALE: Thank you. Mike Tringale,

CHPA. Our survey only included respondents who told us that they used a product with oral phenylephrine, either in single ingredient or combination, in the past 12 months.

DR. LE: Okay. Thank you.

My next question is for Dr. Gelotte; sorry if I mispronounced your name here. On slide 31, briefly, you mentioned the scientific limitation of the study presented by the FDA in evaluating the bioavailability to conclude as one. Actually, I take that back. You mentioned during the presentation of this slide the absolute bioavailability of 38, and there was specific limitations, scientific limitations of this study.

Can you elaborate on that?

DR. HOWARD: Dr. Gelotte?

DR. GELOTTE: Cathy Gelotte. Certainly one of the limitations is what was brought up previously about the infusion rate being over 20 minutes, is one of them. The second limitation is that the study itself, the oral dose and the IV dose was measured in different individuals.

Typically, what we do today would be a crossover design, so that would be the second. And the third is when a figure was brought up showing the IV and the oral dose, that the oral dose seemed to have concentrations for 1 milligram that was similar to 10, so that's sort of suspect of what's going on there.

So those will be considered limitations, and that's why this value is probably unreliable, but there are no reliable data to estimate the absolute bioavailability.

DR. LE: And I have a few other follow-up questions for you, so if you can remain there, that would be great. Also on the same slide, actually slide 31, you have listed there a high volume of distribution of 24.8 liters. I wanted to know, do you have data specific to the site of action of how the distribution is, as site of action in the nasal mucosa?

DR. GELOTTE: No, we do not. The volume of distribution here is called a parent because it's divided by F. So in other words, if we don't know

F, we don't know what the number is. What information we can get from a very high volume of the distribution is that if it's more toward the concentration of the volume of the human body, it would be a smaller number. A large number tends to mean it goes out to the tissues, but we cannot measure what those concentrations are.

DR. LE: So that number, while high, we don't know if it's actually getting to the nasal mucosa; correct?

DR. GELOTTE: Oh, no. Phenylephrine is in the nasal mucosa, but you can't measure it, so we don't actually take tissue and measure it there. We can only measure what's in the plasma in the pharmacokinetic study.

DR. LE: Correct. But do you know what the penetration is? For example, for a bone infection, we would try to estimate what's in the bone and the serum, and get a ratio from there. Do you have any thoughts mechanistically in the penetration of nasal mucosa and the amount?

DR. GELOTTE: No, we do not.

DR. LE: Okay. Then slide 33, I know the limitations, and I do agree with you, and I think Dr. Figg mentioned before about the use of a consistent variable, either total drug or total drug and metabolite, given that both the red and the blue line would be similar in terms of what is measured.

Now, I want to ask, let's say if the blue line also included metabolites, for example, I'm trying to figure out if the metabolites happened to be active metabolites rather than inactive metabolites, how would you go about measuring bioavailability?

DR. GELOTTE: Well, what's done nowadays and now in the current assays, you really need to measure the active moiety or the particular gradient. So you would not be measuring a mixture, so the assay right now can measure phenylephrine. You would need to conduct the study with IV phenylephrine and oral phenylephrine, and measure just the parent phenylephrine to actually get that number, and that does not exist.

DR. LE: Right. But what if you had active metabolites, would that change at all? Would you measure that in addition to, but have it as a separate measurement?

DR. GELOTTE: Yes. If it's measurable and quantifiable, and oftentimes it can be, you would also measure the active metabolite. So that wouldn't be a bioavailability number; that would be what is the relative bioavailability or the conversion. So we wouldn't be looking at absolute bioavailability for phenylephrine or a drug, a parent.

DR. LE: Okay. And then my last question for you would be slide 39. This was very helpful. I really like this slide in terms of showing -- I believe you presented this -- the data here. I'm just curious -- because it was mentioned that the sample size for many of these studies, I think one was 88, and the rest were less than 25 or so -- what the standard deviation bars of these time points would look like to kind of show the spread of the data.

Can you provide some thoughts on that? Maybe it was you, or maybe Dr. Druce can comment.

DR. GELOTTE: Yes. I believe we have some of these curves in Dr. Druce's presentation, where the error bars are shown. I don't know if we want to bring up one of those, please, in the core.

While they're bringing it up, besides that, is there anything else you want to ask about the slide until they locate that one?

DR. LE: I think that's what I just wanted to ask in terms of the standard deviations for some of these time points that were listed here to kind of better show the variation in what we have.

DR. GELOTTE: Okay. Here is one slide that shows the variation in the nasal airway resistance for 10 milligrams, 16 subjects, that shows the, I believe, standard error.

DR. LE: Do you have it for all the other studies? Because this is the Elizabeth 2, correct?

DR. GELOTTE: Here's another one; so there's more variability in this particular study.

DR. LE: Okay. It seems like there is quite

a bit of variability. Okay. I think those are the only questions I have for you related to your slides there. I do have questions for Dr. Druce.

DR. HOWARD: Okay. If you'll pose your question while he is coming to the podium.

DR. LE: Sure.

DR. COYLE: Dr. Le, I might ask this be your last question just so that I can move on --

DR. LE: Okay.

DR. COYLE: -- to another members of the panel as well.

DR. LE: I will. This will be the last question.

So it's clear that you have favor for the use of NAR as the more favorable primary endpoint since it is objective, and I agree with you for the need for an objective endpoint, just as, for example, I would want a blood culture to confirm resolution of bacteremia in an infected patient. A blood culture is a gold standard and highly likely to provide definitive results, so I'm trying to ascertain what the nasal airway resistant task is

appreciating, the user variability and the reproducibility of such a task.

If you can comment on that, that would be great.

DR. COYLE: Yes. Howard Druce. Can you pull up slide AA-8, please?

One of the important things, as you mentioned, is the advisability importance of an objective measurement, and really we're talking about what's going on at the time. We're not talking about 8- and 12-hour reflective measurements. On this particular slide, for the objective measurements in several of these studies, we show a plot between the nasal airway resistance and the subjective score.

Now, this is not a reflective score; this is an instantaneous subjective score, so this is intended to mirror what happens with these particular sufferers. There are people that get transient, sudden, short-term congestion, and you measure what's there at the time when it is, and not for somebody who's got established congestion

throughout the season.

DR. LE: Okay. Can you provide more comment in terms of how this is done, who does it, and is there a coefficient of variation for such a test?

DR. DRUCE: Rhinomanometry, as I showed in previous slides, there are different techniques, which they answer different questions. The most common technique, which is anterior rhinomanometry, in some of these studies, none of which -- or rather, in some of the studies which didn't really drive the efficacy at the panel review -- for example the Bickerman study -- they were developing techniques. But there are standard machines now that are made to measure anterior rhinomanometry, and these can be deployed in wider contexts when necessary, so that's one thing.

Number 2, there is a correlation, as you've seen, between the objective measurement and the short-term or instantaneous congestion method. Yes, it's a matter of training, but the same is true for other measurements such as pulmonary function, other objective measurements.

DR. LE: Okay. Thank you. That's all.

DR. COYLE: Thank you. Thank you both.

I'm going to call on Dr. Clement. Please go ahead.

DR. CLEMENT: Yes. Can you hear me?

DR. COYLE: Yes. Please state your name for the record.

DR. CLEMENT: Yes. Steve Clement, Inova Health System, Northern Virginia. Being the endocrinologist, I'm on a steep learning curve, but I'm getting a lot of information on this.

Dr. Druce, I wanted to address my question to you if you're still close by.

DR. HOWARD: He is.

DR. DRUCE: Yes?

DR. CLEMENT: I really enjoyed your presentation, and your slides were great, and the description of the physiology I think was very helpful. You had mentioned the rhinomanometry -- I may have said that wrong -- as the most widely used measure of clinical trials in this area. Can you just give me an example? I mean, we've got the

data from the FDA saying that the Merck Schering-Plough studies they stated were the biggest studies to date in this condition, and didn't use it. So I'm just curious. What studies are you talking about?

DR. DRUCE: Right. Howard Druce.

DR. CLEMENT: Yes.

DR. DRUCE: You know, this is quite right, and as you've heard from the FDA, they do not accept the validity of nasal airway resistance in this particular measurement, so really it's not surprising one would not submit an application with this particular type of technology. The technology has been used widely in other parts of the world, in Europe, and the other thing that I would note is that, really, there haven't been any recent submissions, to the best of my knowledge, for single-entity decongestants.

So if you are only going to address that one endpoint, which is relevant here, this is the measurement specifically for that, and not necessarily for composite nasal scores for seasonal

allergic rhinitis.

DR. CLEMENT: Okay. One last question, and then I'll be done. It looks like there are a lot of other questions.

Based on your interpretation of the Merck Schering-Plough data -- and tell me if I'm wrong -- you're saying this is the wrong subset of patients to do because these are chronic patients that are less responsive to any drug.

Is that what you were saying?

DR. DRUCE: These patients I say are less responsive to alpha adrenergic agonists, and not necessarily responsive to other drugs such as intranasal antihistamines, intranasal steroids, et cetera. So there are other conditions for which, as you've heard from the FDA, they are used. However, again, these are not substitutes for primary efficacy measurements. They provide adjunctive evidence [indiscernible], as it will stress the system.

When these chambers were developed, and when they were utilized in 2005-2008, the amount of

antigen that that was introduced into the nose at a single time was, first of all, after nasal priming with repeated doses and more antigen than you would ever inhale during a complete allergy season. So there's been an evolution in the technology even within the use of challenge chambers. So again, my conclusion, yes, is that for this particular drug, for this particular indication, this was the wrong application of clinical trial model.

DR. CLEMENT: Okay. Thank you very much. That's my last question.

DR. COYLE: Thank you. Thank you both.

I'd like to call on Dr. D'Agostino. Please go ahead.

DR. D'AGOSTINO: Hi. Yes. This is Dr. D'Agostino. My question I think is going to be for Dr. Howard. You spoke about how there would be implications on consumers, particularly potentially drug shortages and supply chain issues. I was wondering if you could elaborate on that.

DR. HOWARD: Absolutely. I'll ask Mr. Spangler to also provide additional context,

but as we talked about pseudoephedrine, while it is an OTC oral medication, it is only sold behind the counter because of the risk of diversion to convert the pseudoephedrine to methamphetamine, so there are additional restrictions that apply to OTC products that contain pseudoephedrine.

MR. SPANGLER: David Spangler, Consumer Healthcare Products Association. Yes, in addition to what Dr. Howard just mentioned, very specifically, if you do want to change to pseudoephedrine, one, you would need to be already licensed with DEA. If not, you'd have to be applying, have to institute certain security controls, compliance with state law requirements, and then you would have to request your quota. Quota requests go in in the spring, manufacturing in May, procurement in April. You would then get your quota, then, some months later.

Then as a practical matter at the retail level, typically they're doing their planograms, i.e., what the store is going to look like. Those get adjusted in the spring and then implemented

typically in the fall in most major retailers. So you're going to get significant lag, plus, as Dr. Howard mentioned, there's a limit on the number of products that a retailer would be willing to carry behind the counter because of limited space.

DR. D'AGOSTINO: Thank you. That's helpful.

In addition to impacts on pseudoephedrine, would you anticipate additional impacts on other products in people who maybe wouldn't go to pseudoephedrine but would go to things like intranasal, phenylephrine, or other allergy medicines? Could you see downstream effects, and could you elaborate on what those might be?

DR. HOWARD: Yes. There is a potential that there would be other downstream effects because, as you said, if people didn't want to use products that contain pseudoephedrine, we showed in our data that consumers prefer to have oral formulations, so they may not choose to use one of the alternate formulations. Also, if other people or consumers decided to purchase some of the other formulations, manufacturing has a certain capacity and may not be

able to ramp up to provide additional products to consumers if there was a conversion to the other products that were provided as alternatives.

I'll also ask Dr. Druce to speak.

DR. DRUCE: Howard Druce. Just a very brief point, and that is that the oral pseudoephedrine 10 milligrams, I used the word "fit for purpose," and I did that deliberately because it does one job; it relieves a stuffy nose. And it's not an anti-inflammatory, it's not an antihistamine, it's not intended for somebody to take constantly throughout an allergy season. You've seen that it can be dosed up to 7 days.

One of the graphic ways that I like to explain that is that nasal congestion, when it's temporary, doesn't hit you on a schedule. It doesn't hit when the pollen count first starts in August for ragweed. So when you can't breathe and you just can't breathe through your nose, I would really defy anybody to see how long they can manage like that without going for something for relief. And if the pharmacy's closed, certainly I would

like to be able to go to the supermarket or the store and get something that would make me less miserable.

DR. D'AGOSTINO: Thank you.

Just one more question.

DR. COYLE: Dr. D'Agostino, I've got a few others waiting, so if you don't mind, I'm going to move on. But please hold on to your question. We may have time to revisit at the end of the day today. Thank you.

I'm going to call on Dr. Ginsburg.

DR. GINSBURG: Diane Ginsburg, University of Texas at Austin College of Pharmacy. First and foremost, thank you and your team for your very informative presentations. I appreciated getting the information.

Dr. Howard, I have a couple questions related to the consumer survey that you presented, specifically slides 9 through 11. On slide number 9 in talking about the demographics, you said that the footnote in the bottom, there was oversampling in terms of ages 50 plus, as well as

rural areas.

Do you have any breakdown of what that is in the 1200 individuals that were part of this study? I'm trying to get a sense of was it a lot of people 50 and older; was it a lot of people in rural areas by virtue of that term "oversampling?"

DR. HOWARD: Okay. I'll ask Mr. Tringale to respond.

MR. TRINGALE: Hi. Yes. Thank you. Our total sample of the population was 1200 adults 21 years and older, and by oversampling, we specifically developed a purpose of sample to get at least 25 percent of the respondents either age 50-plus and in rural communities. And actually, we ended up with 30 percent in rural, so about 360 respondents, and for 50-plus, we had over 300 respondents as well. So they make up the total oversample, which allowed us to do in that subgroup more reliable descriptive statistics on those particular subgroups.

DR. GINSBURG: Stay there because I think you're going to be able to answer -- I have just

two follow-up questions to that and related to that. In capturing that data in demographics, were there any questions related to other conditions being treated or anything that might have had any impact related to their responsiveness to decongestants, to oral decongestants?

MR. TRINGALE: There were not.

DR. GINSBURG: Okay. Sorry. And just one smaller question, then I'll be done.

The questions like on slide 11 and slide number 10, what were the response options with those questions? Was it yes/no? Was it on a Likert scale?

MR. TRINGALE: It varied depending on the question. And actually, the full instrument is included in our docket, so you'll find some of the questions we had multiple choice, and other questions we had more of a Likert scale, exactly.

DR. GINSBURG: Appreciate it. Thank you very much. I'm done.

DR. COYLE: Thank you.

Ms. Schwartzott, we have just a few minutes

for a very brief question, so I'll go ahead and allow you to ask your question, if possible.

MS. SCHWARTZOTT: Yes. I was wondering if I could ask the FDA to respond to one of the statements that the association has made. Is that possible during this part?

DR. COYLE: Ms. Schwartzott, we're going to defer that until a little bit later. We may have an opportunity to come back to ask FDA to respond, but for now, this is CHPA's time.

MS. SCHWARTZOTT: Okay.

DR. COYLE: Dr. Dykewicz, do you have a very brief question you would like to share?

DR. DYKEWICZ: Well, one brief question for Dr. Druce, slide 67, which was on the Horak study, the Vienna Challenge Chamber, that was looking at rhinomanometry.

So looking at that 4-hour period of 240 minutes, when phenylephrine should have been active, we don't see much difference versus placebo. So your explanation, again, as to why we should not look at this as being evidence of lack

of effectiveness, would be what?

DR. DRUCE: Howard Druce. This slide, which was taken from the the publication, does not obviously show any variability data. What we do note, and at that particular time point, is that there really is a sort of crossover between the phenylephrine and pseudoephedrine action curves, and, really, we see separation from placebo. So although there's no statistical significance at that point, it does not indicate to us that there's no activity.

DR. DYKEWICZ: Okay. Thank you.

DR. COYLE: Thank you.

So we will wrap this up. We'll take a quick 10-minute break. Panel members, please remember that there will be no chatting or discussion of the meeting topics with other panel members during this time, and we will resume at 3:00 Eastern Standard Time, or, I'm sorry, Eastern Daylight Time. Thank you.

(Whereupon, at 2:51 p.m., a recess was taken, and meeting resumed at 3:00 p.m.)

Open Public Hearing

DR. COYLE: We will now begin the open public hearing session.

Both the FDA 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 context of an individual's presentation, and 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 industry. For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your participation in 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 relationships 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 this committee in their 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 for 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 chairperson. Thank you for your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

DR. ABUDAGGA: Thank you. I am Azza

AbuDagga, a health services researcher at Public Citizen Health Research Group. We have no financial conflicts of interest. I note that in the context of oral congestion, we petitioned the FDA in 2000 to ban phenylpropanolamine, PPA, due to safety concerns before the agency removed it from the market. We believe that even when safety is not a concern, ineffective drugs should not be on the market.

We concur with the conclusion of the FDA briefing document that the current collective evidence strongly demonstrates that oral phenylephrine hydrochloride is not effective for temporary relief of nasal congestion at the monographed dose of 10 milligrams and at the monographed dosing frequency of every 4 hours, nor at larger potentially safe doses up to 40 milligrams given at the same frequency.

Mainly, the FDA's clinical pharmacologists have confirmed that based on updated technological methods, the bioavailability of phenylephrine when taken orally is less than 1 percent because the

drug is broken down during absorption. These scientists also have concluded that the half-life of oral phenylephrine is significantly shorter than the 4-hour dosing interval.

Additionally, FDA's new analysis of the original efficacy studies of oral phenylephrine uncovered many methodological and statistical problems that make these studies equivalent to phase 1 studies by current standards. Notably, two of these original studies generated unbelievable, near-textbook perfect results that were not duplicated in other similar studies by the same sponsor, according to the agency's scientists. Furthermore, the FDA clinical reviewers examined publicly available data from three adequately-controlled, industry-sponsored clinical trials conducted since the 2007 NDAC meeting.

These trials represent the largest and most well-designed available studies evaluating the efficacy of oral phenylephrine for nasal congestion. They clearly illustrate the lack of efficacy of oral immediate-release phenylephrine at

doses up to 40 milligrams at extended-release doses of 30 milligrams. Based on this current credible and consistent evidence, the FDA scientists concluded that orally administered phenylephrine is not effective at any dose that can be administered with a reasonable margin of safety.

As discussed in FDA's briefing document, the benefits of removing oral over-the-counter phenylephrine from the U.S. market are numerous. These include avoiding unnecessary costs and possible delay in care or missed opportunities for using effective treatments when needed; avoiding potential allergic reactions or other adverse events caused by taking multiple products containing oral phenylephrine; avoiding the risks of the drug's accidental use in children; and decreasing overall healthcare costs.

These benefits outweigh any industry-related consequences of removing this ineffective drug from the U.S. market. Therefore, we urge the committee to vote no on the questions regarding whether the current evidence supports the effectiveness of

orally administered phenylephrine for nasal congestion and whether a higher dosage of the drug would be safe and effective.

In conclusion, oral phenylephrine salts should no longer be classified as generally recognized as safe and effective. Consumers wouldn't be served by leaving these placebo-like products on the market. To allay potential concerns, it's imperative for the agency to couple the removal of oral phenylephrine from the market with disseminating educational materials for consumers and healthcare professionals about the lack of efficacy of these products and the availability of effective treatment alternatives for nasal congestion that require treatment. Thank you.

DR. COYLE: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself by stating your name and any organization that you are representing for the record? You have 20 minutes.

DR. MELTZER: Hello. My name is Eli Meltzer. I'm a clinical professor of pediatrics in the Division of Allergy and Immunology at the University of California in San Diego. I have no financial conflict of interest. I'll be speaking on two subjects. The first subject is about two studies I helped to conduct on the efficacy and safety of oral phenylephrine in the treatment of nasal congestion. Second, I'll review other medications that are available and are used to treat nasal congestion.

The first of the two clinical studies was reported in the Journal of Allergy and Clinical Immunology in practice in 2015. The background for this dose-ranging trial of oral phenylephrine was that efficacy of the usually recommended dose of 10 milligrams was not confirmed. We enrolled 539 adults in 34 sites across the United States with a definitive history of springtime seasonal allergic rhinitis and positive specific IgE to the pollens prominent in their sites, in their community, during that time period. The ages

ranged from 18 to 77.

There was a baseline run-in time which lasted 7 days. The last 4 days were the symptom diary that we used for the baseline, and during that time, the patients took loratadine once a day. The 7 days were also taking loratadine once a day plus 7 days dosed every 4 hours, either placebo or phenylephrine hydrochloride tablets 10 milligrams at dosages of 10 milligrams, 20 milligrams, 30 milligrams, or 40 milligrams.

The primary efficacy endpoint was the mean change from the baseline over the 7-day treatment in daily reflective nasal congestion scores, which was scored on a range of severity from 0 to 3. There were over 100 patients in each of the four phenylephrine groups, 10, 20, 30, and 40 milligrams and 100 subjects in the placebo group. These were analyzed.

In terms of the efficacy results, the mean medication adherence was roughly 80 percent for each of the five treatment groups. The key finding for the primary efficacy variable compared with

placebo, none of the oral phenylephrine hydrochloride treatment groups had statistically significant greater change from baseline in the reflective nasal congestion scores. You can see those numbers. The placebo nasal congestion score was reduced 0.43, 10 milligrams, 0.46; 20 milligrams, 0.50; 30 milligrams, 0.51; 40 milligrams, 0.46, no differences statistically from placebo, and essentially all secondary endpoint comparisons, including nasal congestion at specific times, were not statistically different from placebo for an identified dose of oral phenylephrine. We can see visually here in both the placebo and in the active groups, both during the baseline and during the treatment time, no differences between doses and no meaningful differences between active and placebo.

In terms of safety results, the most common adverse effect was headache at 3 percent not dose related. The 40-milligram dose had one case of chest and jaw pain and one case of moderate increase in blood pressure, but generally no

sustained or dose-related changes in blood pressure. So in conclusion of this first phenylephrine dose-ranging trial, this was a large and well-designed study. It failed to identify a dose of oral phenylephrine in the range of 10-to-40 milligrams given every 4 hours that was significantly more effective than placebo in relieving nasal congestion.

The second clinical study was reported in the Annals of Allergy, Asthma, & Immunology in 2016. The method was similar. This had over 570 adults in 29 sites with, again, an indefinite history of seasonal allergic rhinitis, this time during the fall. They also had specific IgE to pollens that were ambient in that time in the sites that were part of the study.

The baseline run-in was 7 days, during which the patients took loratadine as needed, and that was followed by 7 days taking every 12 hours either blinded placebo or oral phenylephrine hydrochloride modified 30-milligram tablets. The dosing was thought to be, in the modified-release formulation,

more convenient, being only twice a day instead of every 4 hours and provide sustained levels of active parent phenylephrine, and thereby improve efficacy. The primary efficacy endpoint in this study was the same as in the first mean change from baseline over the treatment period in daily reflective nasal congestion scores in a range of 0 to 3.

We see here that the placebo had 287 patients. The 30-milligram twice-a-day regimen had 288 patients, again 29 sites across the United States, a fairly widespread distribution. For the efficacy results, the adherence here was 99 percent-plus for both the placebo and the active treatment groups. The mean loratadine, which was taken as needed, was the same in the placebo and the phenylephrine groups, 3.8 days for placebo groups and 3.8 days for the phenylephrine groups during the treatment phase.

The primary efficacy endpoint is compared with placebo. The oral phenylephrine modified-release treatment group had no statistical

significant greater change from baseline during the entire treatment period in reflective nasal congestion scores. The placebo reduced the nasal congestion 0.41; the phenylephrine a little less, 0.39. Essentially, all the secondary endpoint comparisons showed similar changes from baseline.

One additional outcome was looking at quality of life. Generally, patients with nasal congestion have problems physically, socially, emotionally, and mentally, and quality of life can be measured by the Rhinoconjunctivitis Quality of Life Questionnaire. In this study, there was no difference in the placebo and in the phenylephrine groups in terms of their assessments of their quality of life by that questionnaire.

You can see on the right-hand side, the baseline for the placebo was 2.2 out of a possible 3, and the phenylephrine 2.35 out of a possible, again, 3. No difference at baseline, and after the treatment, 0.41 in the placebo group changed, a reduction in their nasal congestion; 0.39, a little less in the phenylephrine group but, again, not

statistically significant.

In terms of safety, between the two groups, there were no differences in the blood pressure, there was no difference in the heart rate, there was no difference in the frequency of headaches, both about 3 percent, and there was really no difference in what we sometimes see, CNS stimulation with these agents as manifested by insomnia or irritability, no difference between the two groups. And the conclusion was, in this large well-designed study -- and it was expected to provide sustained levels of the active parent hydrochloride phenylephrine -- during the 12-hour dosing intervals, the results showed that although the 30-milligram oral phenylephrine was well tolerated, it was not significantly more effective than placebo in relieving nasal congestion due to allergic rhinitis.

We will now turn from the clinical trials that I've just presented about phenylephrine to the subject of other medications that are options for the treatment of nasal congestion due to allergic

rhinitis. According to a survey of 2000 patients with allergic rhinitis, among the symptoms that they experienced, nasal congestion is the most bothersome of all their symptoms. You can see in this slide, nasal congestion is selected over 50 percent by patients, both adults and children, as the most bothersome symptom, more so certainly than runny nose, sneezing, and itchy nose.

This table is a survey that was done in 2015, around the same time as the studies that I just reported, and this survey had a question related to allergic rhinitis patients regarding which medications they were taking for their symptoms, both over the counter and by prescription, both in adults and in children. And the most common, if you'll look at the left column, was oral antihistamines, and the second most common was oral decongestants.

Further lower on the list in terms of frequency of use was intranasal decongestants, nasal antihistamines, intranasal corticosteroids, and combination agents. I'll show you efficacy of

those families. Unfortunately, despite it being the most commonly used by patients with allergic rhinitis, when you look at the left-hand column, which is the symptom of nasal congestion, according to the most recent practice parameters from the American Allergy Societies, oral antihistamines have limited efficacy as treatment for nasal congestion.

This is a study that compared placebo to the oral antihistamine desloratadine. Certainly, that antihistamine improved the symptoms of nasal discharge compared to placebo, nasal itch, sneezing compared to placebo, but the oral antihistamine did not improve nasal congestion. That was the symptom. The next slide shows what about the nasal flow as measured. In rhinomanometry, which measures both expiratory and inspiratory flow, there was slight improvement in expiratory flow by the oral antihistamine; however, the inspiratory flow, which is really the important functional aspect of the nose, was not improved.

In contrast to oral antihistamines,

intranasal antihistamines do improve nasal congestion. In this study of the intranasal antihistamine azelastine, the nasal inspiratory flow rate improved by 14 percent from baseline, and the improvement occurs rapidly. So when you give intranasal antihistamine to somebody who's congested, generally within 30 minutes there is a decrease in their nasal obstruction, and that is sustained usually for the pharmacodynamic length of time for those agents; rapid onset, adequate improvement.

The oral decongestant phenylephrine I have suggested is not effective; however, oral pseudoephedrine, which is also a nasal decongestant given orally, does improve nasal congestion. In this study, if you look at the four columns on the right-hand side called "overall," the column to the farthest right is placebo. That was the improvement in the symptom of nasal congestion. Next to it, to its left, which is black and white, is Sudafed, and you can see an increase in the improvement of the symptom with the oral

decongestant pseudoephedrine.

Related to what I have reviewed, I'll list a few summary statements from the practice parameters, the consensus-based statements that were published in 2020. First, oral antihistamines were minimally effective for nasal congestion and less so than intranasal antihistamines. Secondly, the oral decongestant phenylephrine demonstrated to be ineffective for reducing nasal congestion. Thirdly, the oral decongestant pseudoephedrine is effective, and if nasal congestion is uncontrolled by an oral antihistamine, considering adding pseudoephedrine to that oral antihistamine would be a worthwhile thought.

Certainly toleration is important. The oral decongestant pseudoephedrine has been restricted to reduce illicit methamphetamine production, and it can cause insomnia, irritability, and palpitations. And lastly, oral decongestants do not cause rebound congestion.

Along with the intranasal antihistamines, which I suggested do improve nasal congestion, and

pseudoephedrine, which I suggested does improve nasal congestion, intranasal corticosteroids are a third monotherapeutic agent known to improve nasal congestion. In the second row of this table, we can see baseline scores for the intranasal corticosteroid mometasone, and we also see one for placebo, and you can see they're both 2.6. That was the rating the patients gave for their congestion. After 2 weeks of treatment, you can see the mometasone reflective nasal congestion score was significantly better. It was 25 percent better in reduction of nasal obstruction. The placebo was only 16 percent improved.

A combination of an intranasal corticosteroid plus an intranasal decongestant is even better than the intranasal corticosteroid by itself for the improvement of nasal congestion. In the third row, we see that the 2-week change from baseline in the peak nasal inspiratory flow improving nasal inspiration shows, if you look from the right-hand side of that third row, placebo was improved 23 percent. The single agent of

mometasone, the intranasal corticosteroid, was improved 41 percent, but the combination of the intranasal corticosteroid plus the intranasal decongestant, oxymetazoline, improved 57 percent when one spray was used and 66 percent when 3 sprays were used.

If we look at the next slide, again some additional practice parameter consensus statements include intranasal corticosteroids are effective for short- and long-term treatment of nasal congestion. Intranasal decongestants are effective, too, including phenylephrine, the one that's not effective orally, for either intermittent or episodic nasal congestion. Short-term treatment is usually 3-to-5 days, medicine given twice a day.

Thirdly, intranasal decongestants can be recommended for persistent nasal congestion unresponsive to intranasal corticosteroids. You can add the intranasal decongestant to the intranasal corticosteroid for up to 4 weeks. It produces faster and greater decrease in nasal

congestion than with either the intranasal decongestant or the intranasal corticosteroid by itself, and when intranasal decongestants are added to intranasal corticosteroids once a day for 2-to-4 weeks, rhinitis medicamentosa does not occur.

The last combination I'll discuss and recommend for persistent nasal congestion, unresponsive to intranasal corticosteroids alone, is intranasal corticosteroids plus an intranasal antihistamine. In the middle column, we see that the combination of the intranasal steroid fluticasone and the intranasal antihistamine azelastine is statistically better not only than placebo, but also the individual components of fluticasone as monotherapy and azelastine as monotherapy.

In conclusion, the bad news is oral phenylephrine is not effective for nasal congestion; however, the good news is there are many fine therapeutic options for nasal congestion due to allergic rhinitis. Thank you.

DR. COYLE: Thank you. Thank you, speaker number 2.

I will just pause for a moment to see if there are any brief questions from the advisory committee members, given that we've seen some new data here today.

Yes. Dr. Figg, go ahead.

DR. FIGG: Thank you for that presentation, very, very nice and very enlightening. Your conclusion is that pseudoephedrine has no effect.

DR. MELTZER: No, no, no, no, not pseudoephedrine. Pseudoephedrine --

DR. FIGG: I'm sorry. Phenylephrine. I'm sorry. I said that incorrect. I'm trying to get to the point. Who funded these studies? Merck?

DR. MELTZER: Correct. Merck funded the phenylephrine studies. They were looking to see if they could come up with a longer acting phenylephrine. Phenylephrine was only available at the time that we did the studies in the short-acting, every 4-hour regimen, and that is from an adherence standpoint very difficult for

patients; so if they could create a modified -- the other issue they had was, what is the right dose? We didn't have any good studies of what the right dose is. So the first study was to find a dose. We went double, triple, quadruple, and showed no benefit, and then we tried the modified release, and showed no benefit.

DR. FIGG: And who was the co-author, and where did they work on both of those studies?

DR. MELTZER: Yes. The three authors that are listed in both of those studies are myself -- I am a practicing clinician and do clinical research -- Paul Ratner, who unfortunately has passed away, and was a clinical researcher and a clinician in Texas, and the third was Tom McGraw, who worked for Merck.

DR. FIGG: And Merck did not try to stop the publication of these papers?

DR. MELTZER: Not at all; not at all. I was very happy about their attitude. They said that's the science, those are the data, publish.

DR. FIGG: Thank you.

DR. COYLE: Thank you.

I'm going to call on Dr. Clement, and do please remember to state your name into the record for me. Thank you.

DR. CLEMENT: Yes. Steve Clement, Inova Health System in Virginia. I'm the non-allergist/ pulmonologist in this group, so I'm still trying to learn everything. One of the speakers on the industry group was very emphatic when he was reviewing your study that SAR is not the cold, and that they're completely different.

You mentioned that you're a clinician, so how do you respond to that? Do you think these data would be replicable in a study of patients with just average cold? He was saying that the SAR is much more refractory and difficult to treat compared to a common cold, which may still benefit from even mild efficacy.

DR. MELTZER: There's about six questions in there, with all due respect.

DR. CLEMENT: Appreciate it.

DR. MELTZER: Common colds are different

than the allergic mechanism. The allergic mechanism is not more difficult or less difficult; it depends upon the individual patient. But congestion is congestion, and the etiology of it, whether it's infectious or immunologic, is comparable. I think that what works will work for congestion, whatever the etiology happens to be. I think the magnitude of the disease determines the efficacy.

DR. CLEMENT: Okay. Thank you very much. That's my only question. I appreciate that.

DR. MELTZER: Sure.

DR. COYLE: Thank you. Thank you very much.

I'm going to move on to speaker number 3. Speaker number 3, please unmute and turn on your webcam. You may begin and introduce yourself by stating your name and any organization that you're representing for the record. You have 15 minutes.

DR. HATTON: Thank you for this opportunity. My name is Randy Hatton. I'm a clinical professor at the University of Florida, College of Pharmacy, where I've been for over 40 years. I'm not here

representing the University of Florida; I'm here representing myself as a private citizen.

I've been interested in this topic for over 20 years with my colleague Leslie Hendeles, who you'll hear from a little bit later. I got interested because I was the director of the Drug Information Center, and after pseudoephedrine was removed in front of the counter to behind the counter, I received a rash of calls from around the state of Florida, asking why oral phenylephrine didn't work. That led me to Dr. Hendeles, and the two of us have collaborated on this issue for over 20 years. I don't have any conflicts of interest, as is stated on the slide.

Let me state very clearly, there is no modern evidence that shows that oral phenylephrine is effective. Our meta-analysis, published in 2007, questioned the effectiveness of oral phenylephrine. There's a competing meta-analysis flaw I'll talk about a little bit later, but those meta-analyses do not prove efficacy or that there is no efficacy. The several modern studies that

came after the 2007 advisory committee meeting show that oral phenylephrine is not effective. The reason it's not effective is because not enough phenylephrine gets to the site of action in the nose, so therefore, oral phenylephrine should not be deemed effective and should be removed from the market.

You've seen this forest plot a couple of times. This is from our original publication back in 2007, where we asked, through the Freedom of Information Act, to get the raw data that was used by the original monograph for oral phenylephrine. One of the things I'd like you to take from this slide is heterogeneity. Those of you that know meta-analyses know that heterogeneity is the enemy in meta-analysis. We were looking at this to see whether there was a suggestion as to whether or not oral phenylephrine worked. As you can see, our 95 percent confidence interval crossed zero, and we questioned the efficacy of the 10-milligram dose of oral phenylephrine.

Because there was so much heterogeneity, we

looked at the different labs that did these studies way back in the 1960s and 1970s. What we found was a highly suspicious trend in the Elizabeth Biochemical studies. As I've shown on this slide, if you just look at the bars with the crossed lines, those are the Elizabeth studies at 10, 15, 20, and 25 milligrams. Interestingly, there was no dose response for phenylephrine from the Elizabeth Biochemical labs. That led us to do some additional analysis.

Our statistician, Dr. Jonathan Shuster, he examined the raw data from the Elizabeth Biochemical studies. Dr. Shuster's analysis suggests either a poor methodology for Elizabeth Biochemical, an unusual patient population, or fraud. And this table, table AII, shows you that over 24 percent of the final digits, the last digit, had a frequency of 5, which according to the method of Buyse, listed on this slide, suggests that this should not happen by chance; that there is something wrong with these data.

This slide that comes from the Elizabeth

Biochemical study shows no placebo response, another highly unusual finding. Other than Elizabeth Biochemical, the Cintest number 1 found a positive response. Notice there were two other studies done by Cintest that were negative studies. This study is interesting because we couldn't do forensic statistics on that because of the way the data was presented, as percents rather than the actual values, but if you look at the results in the figure on the slide, you'll note that the measurements of nasal airway resistance don't match the pharmacokinetics of oral phenylephrine, with the peak occurring at about 3 hours, and I think you've heard multiple times today that that is not reasonable for a dose of oral phenylephrine.

Next, we have the Huntingdon Research Center study number 1. This study was done to try to replicate what was found in Elizabeth Biochemical, which as discussed earlier today, they actually went to Elizabeth Biochemical because they couldn't replicate what they were finding at their study, and they were unable to validate Elizabeth

Biochemical studies, and they also noted the small variability in the Elizabeth Biochemical studies.

So, these old studies, not modern studies like we'll talk about in a minute, but these old studies suffer from many of the same problems. Most were done in the late '60s and '70s. They were not published; they were memos sent to the FDA, and they did not undergo peer review. They were in-house studies funded by pharmaceutical companies. They were very small studies, and they had unusual data, as I mentioned for the Elizabeth Biochemical and the one Cintest study. Also finally, the nasal airway resistance studies that were done back then used old technology, and there is newer technology that could have been used since the 2007 ADCOM committee to show that oral phenylephrine worked.

This study shows the number of patients we're talking about in our meta-analysis who were on oral phenylephrine that had these very large favorable results and highly influenced the overall meta-analysis, whether it was ours or whether it

was the Kollar meta-analysis, and you can see those are very small numbers, less than 50.

I do want to bring up the Common Cold Center at Cardiff University in the UK. This was run by Professor Eccles, who'd been studying decongestants for the Common Cold Centre in the UK for many years. We've been contacted by Dr. Eccles who supports our position that oral phenylephrine is ineffective, and I'm going to quote Professor Eccles here.

"The techniques used to measure nasal airway resistance and the protocols used to obtain nasal airway resistance measurements have greatly advanced since the last data were available for nasal airway resistance for oral phenylephrine that were used in the monograph. Clinical trial design and criteria used to select patients have also greatly advanced, and published studies can be more critically assessed these days."

Based on Professor Eccles' position, he called in an editorial for funding to do modern studies on oral decongestants to show that they're

effective using these more up-to-date techniques. What I've shown on the slide here is the results of one of those studies that looked at oral pseudoephedrine, and as you can see from the figure on the left, those are nasal airway resistance values, and on the right you can see the subjective scores for nasal congestion, and both of those were able to show, using this more modern technique, that oral pseudoephedrine was effective. Now, unfortunately, nobody came forward, and one of my themes in my presentation is there is no modern evidence, like shown for pseudoephedrine, that show that oral phenylephrine is effective.

This is just another Professor Eccles study, and this study again showed that pseudoephedrine was superior to placebo using his more modern types of of technology. Modern studies of phenylephrine like this one could have been done since 2007; however, they have not.

Just to reflect back on what's been reviewed earlier today, what happened at the 2007 advisory committee meeting, 9 out of the 12 members voted

that they wanted new studies, not those old studies from the 1960s and 1970s, which I think we know have some methodological concerns; they wanted new studies. Not only that, but they wanted to have studies that looked at the pharmacokinetics, the pharmacodynamics, and bioavailability. The committee members also brought up the need for -- I stated that already. Sorry. CHPA, or the Consumer Health Products Association, in a statement said that they are committed to adding -- adding emphasized here -- to the existing body of evidence. They have not done so.

We could argue about the methodologies of the different meta-analyses, and our statistician went back and forth with their statistician, but I think one of the most important things you can see here is that whether it's our meta-analysis or the Kollar meta-analysis, the Elizabeth Biochemical studies had a huge effect on the aggregate for both meta-analyses, and we have shown that those data are questionable, at best. For this reason, we're not too worried about which is the better

meta-analysis. We think the modern data have validated our meta-analysis and shown that theirs was not accurate.

So I won't go through this. You've heard all these studies, the Horak, Day, and the two Meltzer studies, and Dr. Meltzer just did a fantastic job, so I won't go over his. But let me just point out that these are published peer-reviewed studies that were published between 2009 and 2016. No similar studies are in the literature, peer reviewed for oral phenylephrine.

This has already been gone over as well. This is the unpublished negative study that was sponsored by Johnson & Johnson that you can find the results for in clinicaltrials.gov. I do want to bring to your attention that even though it was stopped early, the differences in this time frame -- and this time frame is, I think, within 2 hours between the two phenylephrine treatments and placebo -- are so small on this 8-point scale, and the p-values were close to 1, that had a futility analysis been done, I don't care what

sample size you use, there's no way they're going to find a statistically significant difference between placebo and the active comparator.

I do want to point out that on clinicaltrials.gov, you'll see that there's a note. There is an agreement between the principal investigators of this study and the sponsor, or its agents, that restricts the PI's right to discuss or publish the trial results after completion; negative trial results, they could have done a futility analysis, never got published. I also will note that there are several other oral phenylephrine studies in clinicaltrials.gov, and none of those were completed or published, and that doesn't suggest a favorable effect for oral phenylephrine.

I'm really not going to talk about this slide. This is an old study from 1942 that showed a 250-milligram dose of oral phenylephrine showed effects on blood pressure and heart rate, and those authors in their paper stated the threshold doses for phenylephrine in the average adult is about

50 milligrams. I'm also not going to talk about this, but this came from the 2007 advisory committee meeting, and it shows that below 50 milligrams, there's not any effect on heart rate or blood pressure.

Now, there's been some discussion about the Hengstmann oral bioavailability, that everybody has learned incorrectly that it's 38 percent. I want to be clear. The reason why that estimate is incorrect is, because it was done with radiolabeled phenylephrine, it's measuring total phenylephrine of which only a very small percentage is active. Now, this study, although it was said that there is no good data, this good data presented in 2007 by Schering-Plough showed very low levels of total parent phenylephrine.

So oral phenylephrine and low levels in bioavailability, yes, maybe you could have low levels and still have bioavailability, but whether it's 1 percent, 1.3 percent, or less, very minute levels of oral phenylephrine make it to the systemic circulation because of the extensive

metabolism in the gut. And if you look at the publications by Gelotte that you've heard about today, the actual values are very low in the picogram per mL concentrations.

So in summary, I want to say it is important to note that no modern evidence shows that oral phenylephrine at the currently approved over-the-counter dose decreases objective nasal airway resistance or subjective nasal congestion, stuffiness, or pressure measurements. Our meta-analysis of the 1970s suggested that oral phenylephrine does not work, and we pointed out the major flaws in the Elizabeth Biochemical results.

Recent unpublished data, the Johnson & Johnson study and the four published peer-reviewed studies, showed that oral phenylephrine is not effective, and this is due to the low systemic plasma levels that occur after the 10-milligram oral dose, so oral phenylephrine should be removed from the market because it does not work. Thank you very much for giving me this opportunity.

DR. COYLE: Thank you.

I'd like to just spend a few minutes here, if there are any questions from our advisory committee members for this presenter.

(No response.)

DR. COYLE: Okay. Seeing none, thank you very much for your attendance --

DR. HATTON: Thank you.

DR. COYLE: -- and we'll move on to speaker number 4. Speaker number 4, go ahead and unmute, and turn on your webcam. You may begin by introducing yourself, stating your name and any organization that you are representing for the record. You have 20 minutes.

DR. HENDELES: Can you see me? It doesn't look like the video --

DR. COYLE: We can hear you. We can't see you.

DR. HENDELES: Okay.

My name is Leslie Hendeles. I'm professor emeritus at the College of Pharmacy at the University of Florida. I have almost 50 years of

teaching pharmacists and physicians about drugs for asthma and rhinitis. My topic this afternoon is Quality Science Tells the True Story of Oral Phenylephrine.

Can I have the first slide? And I'll move on to the next slide, please. I have no financial relationship to disclose. My take-home messages are, first, oral phenylephrine is ineffective as a nasal decongestant, but safe. Second, 99 percent of the oral dose is inactivated by first-pass metabolism. A 1976 OTC panel reached a specious conclusion about efficacy, and last but not least, there are several truly effective over-the-counter products that are currently available in grocery stores and convenience stores, et cetera, so if phenylephrine is taken off the market, there is plenty to fill its place.

Noted about phenylephrine, many years ago, I read a paper that was presented by Dr. Bickerman to the Proprietary Association, which I think is the predecessor to CHPA, and they had at Columbia University developed methodology that actually was

reproducible with measuring nasal airway resistance. What they did is they added a pneumotachograph to a scuba mask and were able to measure flow and nasal airway resistance, and they compared patients with and without stuffiness. In addition, they had day-to-day variability measured, and they did a reasonable job of showing that they had a reproducible method.

They ended with a double-blind, randomized, crossover design in patients with chronic nasal congestion, comparing placebo, pseudoephedrine 60 milligrams, phenylpropanolamine 40 milligrams, and phenylephrine 10 milligrams. And you can see here this is a change in nasal airway resistance, that both pseudoephedrine and phenylpropanolamine significantly reduced nasal airway resistance, and that phenylephrine was no different than placebo.

There was virtually no -- well, there perhaps was maybe one product or two products with phenylephrine in it after the panel's recommendations. Most of the products had phenylpropanolamine or pseudoephedrine. When the

Combat Methamphetamine Epidemic Act was instituted in 2005, manufacturers did not want to lose their income from their products by putting them behind the counter, so they substituted phenylephrine. There is good evidence that there's phenylephrine in about 261 products, and I have here on this slide that the annual sales is $1.5 billion, but I believe that somebody from the FDA said it was $1.8 billion in 2022.

This is Dr. Hatton's study, and he has done a great job of explaining it. The only thing I will add is a statement. He said, "It's too good to be true." Because of that meta-analysis showing such a striking lack of efficacy, we decided to submit a citizen petition to FDA in 2007, and we requested the FDA to increase the maximum dose of phenylephrine for patients that were 12 years and over. We asked -- [inaudible - audio break].

(Pause.)

DR. SEO: Hello. This is Jessica speaking. OPH speaker number 4, if you are still speaking, we're not able to hear you. Could you please check

if you have accidentally muted?

(Pause.)

DR. HATTON: Yes. This is speaker number 3. Dr. Hendeles is rebooting his computer. If you could just give him one minute, we would very much appreciate it.

(Pause.)

DR. COYLE: Well, I believe we'll be able to offer Dr. Hendeles --

DR. SEO: Hi, Dr. Coyle. Yes, I was going to suggest if we can continue on to the next speaker. We'll keep track of where Dr. Hendeles left off, and then we'll come back to him, if that's ok with you.

DR. COYLE: Yes. That works perfectly.

So speaker number 5, if you're available, please unmute and turn on your webcam. You can begin by introducing yourself, stating your name and any organization that you're representing for the record, and you will have five minutes. Go ahead.

DR. FARRINGTON: Yes. Hi. My name is

Elizabeth Farrington. I am the current president of the American College of Clinical Pharmacy, and I practice as a pediatric pharmacist in both general pediatrics and pediatric critical care, and I have no financial conflicts of interest to report.

The American College of Clinical Pharmacy represents about 17,000 clinical pharmacists, so I'm here, and I'm representing that group. Our mission is to improve human health, but most importantly to demonstrate the safe and efficacious use of medications. Just to reiterate what the previous speakers have told us, the bioavailability of phenylephrine is very low and shows minimal benefit in patients. The bioavailability, although published at about 39 percent, as Drs. Hendeles and Hatton have demonstrated, it's probably closer to 1 percent, and it has been demonstrated in numerous more recent studies to be ineffective as a decongestant.

It's a major ingredient in almost every over-the-counter combination product since the impact of removing agents that could be used to

produce methamphetamine from the market, and published peer-reviewed results clearly demonstrate, as our previous speakers have demonstrated, the lack of efficacy even if you quadruple the dose in the box up to as much as 40 milligrams.

Despite the evidence that phenylephrine is ineffective as a decongestant, the U.S. FDA has failed to remove it from the OTC decongestant monograph, and we would like to ensure consumers that all drugs on the market are effective. There are some small studies that have been published that although the bioavailability is very low in phenylephrine, some patients with hypertension can be quite sensitive to that 1 percent absorption, and there are some case series of stroke reported in adults from elevated blood pressure. There's a series of pediatric patients who became hypertensive from that 1 percent bioavailability, and there is one published study that demonstrated concern in pregnancy as well.

So the American College of Clinical Pharmacy

would like to call on the FDA to remove oral over-the-counter products containing phenylephrine from the market. We feel like there's also adequate other agents -- topical intranasal products -- that can be used for decongestants that are efficacious and that would be more beneficial to patients than allowing them to buy a product over the counter that says it's a decongestant that is ineffective. Thank you.

DR. COYLE: Thank you, speaker number 5. We appreciate it. Thank you.

I'm going to move on. We'll call on speaker number 6 at this point, and then circle back to catch up thereafter. So speaker number 6, please unmute and turn on your webcam. You may begin by introducing yourself, stating your name and any organization that you're representing for the record. You have five minutes.

MS. PHILLIPS: Hello. My name is Sophia Phillips. I'm a health policy associate speaking on behalf of the National Center for Health Research. The medical and public health

professionals at our nonprofit think-tank scrutinize research on the safety and effectiveness of medical products, and we do not accept funding from companies that make those products; therefore, we have no conflicts of interest.

The National Center for Health Research appreciates the opportunity to testify on the lack of efficacy surrounding orally administered phenylephrine, or PE, as a nasal decongestant and the need to reclassify both phenylephrine hydrochloride and phenylephrine bitartrate as not generally recognized as safe and effective.

Our position is simple. Oral PE should not be on the market if it doesn't work. The public needs to trust the FDA to take products off the market that are proven to not work compared to placebo. Here are very persuasive reasons to amend the GRASE status of oral PE: first, to prevent a delay in care, creating missed opportunities for use of more effective treatments, including a doctor's visit if needed; second, to avoid the risks of potential allergic reactions or other side

effects related to use of PE and combination products; third, to avoid the inherent risk, especially for combination therapies, of taking more in order to seek some benefit, as significantly higher doses can lead to negative effects such as potentially clinically meaningful systemic increases in blood pressure; and fourth, to avoid unnecessary costs for consumers and to restore consumers' trust that FDA approval means a product has benefits compared to placebo.

Millions of dollars have been wasted by consumers on a product that has been shown in research to have no more benefit than placebo. The public is being misled and spending their hard earned dollars because of the drug's label specifying it as an FDA-approved effective cold medicine. It is the duty of the FDA to make changes based on the known efficacy of its approved medical products.

We recognize that FDA should educate consumers about research, indicating that PE is not effective and describe alternatives that are

effective, including both oral and intranasal products. FDA should work with the media to explain to consumers how to obtain PSE alternatives from behind the counter. These efforts will be essential to facilitate an efficient transition away from PE toward cold medicines that are safe and effective.

Lastly, FDA stated that the potential impact on industry will not be discussed at this AC meeting. We agree and want to emphasize that the potential to reduce industry profits should be irrelevant when FDA makes decisions that have a direct impact on public health. This is especially true for a product that has been known for years to be ineffective but has not been voluntarily removed from the market by the companies that make or sell it. Thank you for your time.

DR. COYLE: Thank you.

At this time, we will go back to speaker 4. Welcome back. Please unmute and turn on your webcam. Begin by reintroducing yourself, including your name and your organization, and I believe you

have about 14 minutes left for your presentation.

DR. HENDELES: Thank you. Leslie Hendeles, University of Florida. So where I left off was after the citizen petition, FDA arranged for an advisory committee. There were two recommendations from the advisory committee. One was, given the available data that exists, the evidence is supportive -- that's my enhancement there -- that the 10-milligram, immediate-release formulation may be effective. So they weren't very emphatic; it was may be effective. And they said additional studies are needed to assess the efficacy and safety of higher doses.

(Advertisement is played.)

DR. HENDELES: So obviously, the efficacy of what you've seen so far doesn't match what's being promoted to patients, giving them false expectations. Just as an example, this is the Horak study that's been discussed before that shows the relief of congestion in an allergen chamber, where patients got the same allergen at the same dose, and they were randomized to receive

phenylephrine, which is the circle, pseudoephedrine, or placebo. And this is the change in nasal congestions for -- you can see that it was significantly different from placebo with pseudoephedrine but not with phenylephrine.

Dr. Meltzer's already discussed his study in detail. The only thing I would add to his comment is that antihistamines suppress histamine, and nasal stuffiness is not mediated by histamines. So the fact that loratadine was included in his two studies is not likely to have caused a problem because loratadine has no other pharmacologic action than being an antihistamine.

We were so impressed with Dr. Meltzer's study that we then submitted the second petition, and in this one we specifically asked that phenylephrine be removed from the market. This was in 2015, and it was based upon not only efficacy but also clinical pharmacology studies showing that less than 1 percent of the dose of active drug reached systemic circulation.

CHPA mentioned in their briefing that low

oral bioavailability does not mean lack of efficacy. Well, I disagree. I think at least for phenylephrine, it sure does, and the EC_{50}, which has already been shown to, was several times greater than the peak plasma concentration, and therefore it's very unlikely that there was enough attachment to alpha receptors; then, that's really confirmed by, really, five modern, well-designed clinical studies showing that phenylephrine was equal to a placebo.

So for the common cold, there are nasal spray decongestants. Phenylephrine is extremely effective, and I'll show you some data in a second. It's short-acting and there are longer acting products like oxymetazoline, Afrin. There's no risk of rebound congestion with a common cold because the duration of the cold is short-lived, so patients don't need to treat themselves for an extended period of time and, of course, there is oral pseudoephedrine.

For allergic rhinitis, the most effective medications over the counter are nasal steroids,

and there are three different products that are over the counter. Another product is an antihistamine mast cell stabilizer, and the reason why the topical spray antihistamines seem to have more efficacy for stuffiness is because they actually have a mast cell stabilizing effect and prevent the mast cells from degranulating. Azelastine is the drug and Astepro is the brand name; and of course there is oral pseudoephedrine that's combined with antihistamines, and there are three products behind the counter.

This is a study that compares the decrease in nasal airway resistance with topical phenylephrine, which drops down almost 80 percent decrease, and then by 2 hours it's lost a lot of its efficacy. The box, the squares are phenylpropanolamine and less effective than the topical spray but longer duration of action, and then the triangles are a Vicks inhaler, which it's a mixture of levomethamphetamine and camphorin menthol.

This is a study of patients with seasonal

allergic rhinitis that were treated for a month in a double-blind, randomized, crossover design with either fluticasone or loratadine. If you look at the blockage, you can see very clearly that the nasal steroid is much more effective than the antihistamine, and even in perennial allergic rhinitis, for most patients, the over-the-counter nasal steroids are all they need to have relief of stuffiness and the other symptoms as well.

This is a comment that was submitted to the docket by the American Pharmacists Association. It says, "APhA represents our nation's pharmacists, who have tremendous experience with OTC oral phenylephrine products. They often receive feedback from patients who are seeking relief for nasal congestion, relying on claims that oral phenylephrine products will relieve their symptoms. These patients often complain of the ineffectiveness and lack of nasal congestion relief from oral phenylephrine products."

So to conclude, the take-home messages are oral phenylephrine is ineffective. It's

ineffective as a nasal decongestant, but safe. Ninety-nine percent of the oral dose is inactivated by first-pass metabolism, and that makes a difference for this drug. The 1976 OTC panel, although they were well meaning, the studies had many methodological problems and possibly even some fabrication, so they reached a specious conclusion about efficacy. Last but not least, there are several products on the market now that patients can get, and they're sold in grocery stores as well, so they don't have to wait in line or go to a pharmacy and get something, pseudoephedrine, from behind the counter.

I'll stop at this point, and thank you for your time, and especially for accommodating my computer glitch.

DR. COYLE: Thank you, Dr. Hendeles.

I'm going to open up a few minutes for any questions for Dr. Hendeles from the panel.

(No response.)

DR. COYLE: Okay. Seeing none, thank you very much.

Clarifying Questions (continued)

DR. COYLE: As we have some additional time left in our agenda today, we are going to return to take some remaining clarifying questions from earlier today. These can be directed to CHPA or could also be directed to FDA, so please raise your hand. Remember to state your name for the record before you speak and to direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. And as a gentle reminder, it would be helpful to acknowledge the end of your remarks or your questions with a thank you, and the end of any follow-up questions with, "That is all for my questions," so that we can move on to the next panel member.

I'm going to scan my roster here, and we can begin with Ms. Schwartzott. If you had a question remaining from earlier today, I'm going to give you an opportunity to speak, and then we can go back to our roster here.

MS. SCHWARTZOTT: My question was actually

about the --

DR. COYLE: Please state your name for the record.

MS. SCHWARTZOTT: Jennifer Schwartzott, patient representative.

DR. COYLE: Thank you.

MS. SCHWARTZOTT: My question was towards the FDA in regards to the concept of the bioavailability and the efficacy, and it was also brought up by some of the people that were speaking.

I'm a patient, so I'm not a doctor or scientist, so this is something that was confusing me because I'm hearing differences from both sides. I was wondering if the FDA could address the association statement that the low bioavailability or potency does not mean that it's not -- or it doesn't affect the efficacy. I'm sorry.

Could the FDA address that?

DR. MICHELE: Hello. This is Dr. Theresa Michele at the FDA. I'm going to put this in patient-friendly terms, and then I'm going to turn

it over to Dr. Ren, who will give the more precise answer.

So in patient-friendly terms, the thing that matters when you are dosing a drug is how much of the drug gets to where it needs to be and whether it is a high enough concentration to affect the receptor that it's trying to affect to make the change. So in this case, we need the drug to get to the alpha receptors in the nose so that they can constrict the blood vessels and reduce the amount of congestion, so the actual amount that's absorbed is somewhat irrelevant. What we really care about is the fact that the concentration that affects the receptors is higher than the concentration that you can get into your body because it's extensively metabolized by the intestine.

So I'm going to turn it over to Dr. Ren, and he can give a more precise answer.

MS. SCHWARTZOTT: Thank you.

DR. REN: Thank you, Dr. Michele. That's a very good explanation. I'll try to use the plain language as well.

Here, as a pharmacologist, we believe if a drug works, that means it should work at the site where it's working. For nasal congestion, we believe that how the drug works at the nasal congestion is at the nasal mucosa. The amount of the concentration of the drug that's following oral administration should reach a certain level to be efficacious or at least as potent as those animal studies, cellular studies, molecular studies are, indicating that concentration should work. The results show that following the oral administration route, the amount of the phenylephrine, or the concentration of phenylephrine, failed to reach that threshold concentration from the in vitro or cellular level.

There was concern raised in the morning by saying, hey, phenylephrine has a very wide tissue distribution, which means when phenylephrine enters the human body, there could be some other organs which can absorb this phenylephrine so that it can be enriched in certain organs -- I shouldn't use enriched, but distributed to those organs and bind

to something -- but there's no evidence to showing that the nasal mucosa, this tissue, can enrich phenylephrine's amount of concentration at that local site.

In addition, as a pharmacologist, we believe that how this phenylephrine works is through the adrenergic receptor, which is located in the blood vessels; and therefore, in this scenario, the organ concentration or irrelevant tissue distribution concentration doesn't matter here. What matters here is the blood concentration, the plasma concentration. Everyone here in this field measured plasma concentration, and it's lower than the EC_{50} value. So that's why, from a pharmacology perspective, we can provide this evidence to support or explain the lack of efficacy from the clinical trials.

MS. SCHWARTZOTT: Thank you.

DR. REN: Does that clarify your question?

MS. SCHWARTZOTT: Yes, I'm understanding it, but I wanted to clarify it because that's what I thought. Thank you.

DR. REN: Thank you.

DR. COYLE: Thank you.

I'm going to call on Dr. Clement. Please go ahead, remembering to state your name for the record.

DR. CLEMENT: Yes. Steve Clement, Inova Health System in Northern Virginia. I have a question for the FDA. It could be -- I'll leave it up to you -- either Dr. Starke or any of you.

When I got the binder and started reading all this information, frankly, I was shocked, and what I was shocked about is what took so long, as these data were available on the lack of efficacy studies in 2015, and we're pretty deep into almost 10 years, almost 8 years.

So I'm just curious. Why does it take so long? I mean, I was a little disturbed why this didn't come to the surface earlier.

DR. MICHELE: Thank you, Dr. Clement, for that question. This is Terry Michele, Nonprescription Drugs. So, unfortunately, science is a slow process, and the regulatory process is

also a slow process. One of the things that we're particularly excited about under monograph reform is it does give us the opportunity to move things along a little bit more quickly. But what we do with the data is we allow it to accumulate, so that's what we've done with this, and I'm delighted that we now have the data that was asked for by the committee back in 2007, and we're pleased to be able to bring this forward for public discussion so that we can really hear the thoughts of the committee on what these data show. Thank you.

DR. CLEMENT: Thank you very much.

DR. COYLE: Thank you.

Maria Coyle here. I'm going to ask a question of CHPA, and this is in regards to a slide that was presented by Mr. Mullin, slide 78, but it may be a question more for Dr. Druce as a clinician.

When reviewing the meta-analyses that are represented on slide 78 of your presentation, the estimated treatment effect for phenylephrine in both cases was reported at around 10 percent, a

10 percent change in the nasal airway resistance. And my question is just simply, is this clinically significant? Is there any way to know that this relatively small change, from my perspective, as someone who is not maybe as familiar with this measurement or working directly with patients in this area, and who's not familiar with this objective measurement, is this meaningful?

DR. HOWARD: Okay. I'll ask Mr. Mullin to start, and Dr. Druce to provide scientific commentary, if he has any.

MR. MULLIN: Thank you. Chris Mullin. The rationale for reporting the slide with 10 percent -- and I'm referring to that because that's what's available -- we don't necessarily have a responder analysis available to speak to that issue. But I would note that a small difference in means can actually be consistent with a substantial shift in two groups, leading to differences in percentages between patients receiving a degree of relief.

But I think Dr. Druce can speak to the

clinical question. In particular, I think his slide CO-60 that he may display does speak to some of the clinical relevance of those studies.

DR. HOWARD: And as Dr. Druce is approaching, may we share our screen? Thank you.

DR. DRUCE: Howard Druce. At the time these studies were done, there was no requirement, pre-requirement, to prespecify what was a clinically important difference or minimally important difference. It was generally understood that for rhinomanometry, 15 percent changes in nasal airway resistance would be appreciated by patients. In fact, if we take the largest of the studies that were done -- this is, in my view, the best way to look at this, which was the Cohen study -- there were three different methods that were applied to looking at clinically meaningful difference. And whether you use the methodology of Barnes or of Norman, I'm not an expert in biostatistics, but with these two different standard methods of calculating and looking at that, these time points, not only were they

clinically significant, but they correlated with the instantaneous -- these are instantaneous subjective assessments.

DR. COYLE: Thank you.

May I ask just one follow-up question? Maria Coyle again. Are you saying that you believe for your patients, a 10 percent change would be clinically meaningful?

DR. DRUCE: I'd like to draw the distinction that when you say, for my patients, as an allergist seeing patients with seasonal allergic rhinitis throughout the season, that's a different issue. For people who do not need to come to a healthcare provider and have temporary nasal obstruction, it's clear to me that that sort of clinical effect is perfectly adequate to treat their symptoms.

DR. COYLE: Thank you. I appreciate that. Thank you.

DR. HOWARD: And if the chair share would allow, Dr. Gelotte would like to also provide some additional context to the bioavailability question that was asked.

DR. COYLE: Sure. Go ahead.

DR. HOWARD: Thank you.

DR. GELOTTE: I guess to answer the question, when I first heard that the bioavailability is 1 percent, that was discussed as as what the bioavailability is, we really don't know what it is, and I think we do have some data that I'd like to go over.

First, before going over that, in a few of my studies that you have seen today, we have also looked at the metabolites in the urine. The metabolites give you an idea of what's going on, so it is not 1 percent and 99 percent through pre-systemic metabolism, which would be the sulfate metabolite; that's only 47 percent that we determined in the urine. The other major metabolite is through monoamine oxidase, which makes 3-hydroxymandelic acid, and that's about 25 percent of the urine. So that represents phenylephrine that was circulating in the plasma concentration before it was metabolized. So having 1 percent, we really don't know what the

bioavailability is. There really is no good data.

Now, I'd like to return to this slide once again because I think it's a really important slide because we hear the word "potency." The in vitro potency is because the clinical concentrations that we measure in the plasma can't be effective because it's lower than the potency measured in vitro. Remember, potency measured in vitro is a closed system, so you add a concentration and you look at some type of effect, but it's closed. What we have in the body is an open system, where plasma concentrations and the drug is circulating around.

I'd like to bring your attention once again to the table, and you can sort of get a sense of how complicated this might be. If you look at montelukast, where you see plasma concentrations, if we were going to measure in the bound, is about 153 bound circulating in the plasma, but circulating in the plasma is unbound drug, which for montelukast is only 0.31 nanomolar, which is lower than phenylephrine circulating around. Drug theory is that unbound drug is what can leave the

plasma, go to the site of action, and attach to a receptor. Bound drug, even if it's not metabolized or it's an unmetabolized form, cannot leave. So you can see that phenylephrine has an unbound plasma concentration based on the pharmacokinetic data of 1.29.

So again, there's a lot of complexity going on here, and I think the bottom line is we really don't know what the bioavailability is, and 1 percent is not an appropriate number. Thank you.

DR. COYLE: Thank you.

We'll go on and and move on. I'm going to call on Dr. Pisarik with a reminder to state your name for the record. Thank you.

DR. PISARIK: Paul Pisarik. I have a question for the CHPA on their survey of consumers. When I ask the patient what they're taking for their cold or allergy symptoms, a lot of times I get, "I'm taking Mucinex." And I ask them, "Well, what type of Mucinex?" And they have no idea what type of Mucinex they're taking, and there are 15 varieties of Mucinex.

So in the survey, how accurately were these patients' recall as to what they took? How do they know they took something with a decongestant in it?

DR. HOWARD: Okay. I'll ask Mr. Tringale to approach.

MR. TRINGALE: Thank you. Hi. Mike Tringale, CHPA. So we were very careful, to your point about making sure we very narrowly identified this purpose, of the sample of people who had actually used a product with PE. So again, in the briefing materials is the full instrument, but I'll read the question, the screening question we used to try to get to that specific patient population.

We said, "In the past 12 months, have you used any medicine that you can buy without a prescription, also known as over-the-counter or OTC medicine, that you take by mouth, that includes treatment for symptom relief of nasal or sinus congestion due to cold or nasal allergies, often referred to as stuffy nose?"

In addition, we also gave them examples of actual products to further ensure that we got

patients and consumers who actually used those specific products, either singular ingredient or combination, that included PE.

DR. PISARIK: Thank you.

DR. COYLE: Thank you.

We'll call on Dr. Ginsburg. Please go ahead.

DR. GINSBURG: Diane Ginsburg, University of Texas at Austin, College of Pharmacy. My questions are also to CHPA, specifically to two comments that Dr. Druce made through his presentation, and I want to make sure that I'm interpreting these two statements correctly.

Dr. Druce, the two comments that are sticking with me right now is you made the comment that the studies and things that were done in the past met the regulatory requirements at that time, and obviously since 2007 and forward in the studies, as we've gotten more information, are you stating that just because it met the regulatory requirements at that time, that we should just accept that information today, knowing that we have

more information? And perhaps I'm misinterpreting how you were meaning that.

DR. DRUCE: Thank you. Howard Druce. I'm not a regulator; I'm a clinician and I'm a researcher. My interpretation of the data is that the product has a labeled indication for temporary relief of nasal congestion, and that the data that was analyzed by the panel, the committee, and has been reanalyzed multiple times, addressed the drug and that specific indication, as on the label.

The data that has been amassed since 2007 in the seasonal allergic rhinitis model looks at people who have already been diagnosed with seasonal allergic rhinitis and have sustained nasal congestion to be able to enter the trials. In other words, when I look at the body of data, what I see is a certain amount of data that supports a labeled indication, and I see other data, which is interesting, but to me does not address the question of whether this product is effective for its indications.

DR. GINSBURG: I appreciate that, sir. I

have one more question for you, if I may, related to another statement that you made, and this is getting, I think, to the heart of your being a data person as well. You made the comment -- and again, I want to make sure that I read this correctly. You said that the clinical study design wasn't relevant, and I would like to know what you meant by that. And that's my last question. Thank you.

DR. DRUCE: Yes. So what I mean is the following. If we are simply looking at allergic rhinitis or allergies, which we're not because we have a dual indication for the common cold and upper respiratory viral infections and we have upper respiratory allergies -- and you've heard from Dr. Meltzer, as well as me, that the mechanism of action of decongestion is the same.

We're looking at temporary nasal congestion. In other words, if you look at people that have sustained congestion and you look at 12-hour endpoints in sustained congestion, it's interesting but it's not the population for whom this drug is intended, so that's why I would characterize that

as not relevant. I think it's interesting. I think it answers some questions about people who are already diagnosed with seasonal allergic rhinitis, but it does not address those people who are quite well treated and derive benefit without seeing a healthcare professional.

DR. GINSBURG: Thank you, sir, for answering my questions. I appreciate it.

DR. HOWARD: One thing I'd like to add, if I may --

DR. COYLE: Sure. Please state your name for the record.

DR. HOWARD: -- yes. Marcia Howard.

DR. COYLE: Thank you.

DR. HOWARD: There was a question raised about the scientific rigor today versus that from when the monograph studies were evaluated, and we certainly do agree that science continues to advance but that does not necessarily mean that the older studies should be -- that they no longer apply or that those studies should necessarily be run to the standards of today's time.

DR. GINSBURG: Thank you.

DR. COYLE: Thank you.

We're going to move on to Dr. Le. As we do so, or as I call on her, I just want to encourage any other panel members who might have questions to go ahead and raise your hands and get in the queue, particularly if you have not had a chance to ask questions or to clarify comments from either FDA or CHPA as we move into this final 30 minutes of our meeting.

So, Dr. Le, you may begin.

DR. LE: Yes. Jennifer Le from the Skaggs School of Pharmacy, UC San Diego. This question is for the FDA, any member. I'm trying to wrap my head around this, and I've been on the advisory committee for FDA for four years now, and this is the first time, actually, I have become very concerned about the public health and safety perspective in relation to some of the published studies that led to the original approval, the GRASE status of phenylephrine. Of course, this underscores the utmost importance of data

integrity, where data should be complete, consistent, accurate, trustworthy, and reliable, and the need for thorough review, in fact, of data integrity before approval.

I'm curious as to what the FDA does now in terms of policies and procedures, and I know there's the International Council for Harmonisation and good clinical practice standards, their guidelines, but I'm curious as to what the current policy and procedures are for ensuring and maintaining data integrity; and also, if there are allegations that have forensic statistical analysis provided, are there any repercussions that are integrated in this?

DR. MICHELE: Hi. This is Dr. Michele. I'll take that question. I'm going to dissect it a little bit because you've actually asked quite a few questions embedded in one. The first question I believe you asked is what are current practices at FDA for reviewing data and ensuring data integrity of the data that have been submitted?

Is that your first question?

DR. LE: That is correct.

DR. MICHELE: Alright. So currently, FDA reviews data, and when we do that, we look for a number of things. We generally review the primary data from the study when we can get it. When we can't, we will review peer-reviewed journal articles, but in all cases, we require that there is sufficient information in the study reports for us to make an independent assessment of those data. When we get full clinical trial data for an NDA, we will typically do inspections of the clinical trial sites that is guided by our statistical analysis of the data, and we will choose representative sites to visit and have actual audit of those sites.

For the monograph, we're looking at peer-reviewed articles most frequently, but we also do look at data that are submitted that are full clinical trials. And certainly anytime there is a question of data integrity, we would do a for-cause audit of that particular site. Now, what happens, depending on what is found, is a compliance determination, and I'm not going to get into it for

the purposes of this meeting because it's really not relevant. But what we do do is then the statisticians go back and look at the trial to make a determination of whether those data can be thrown out and the trial still maintains its integrity if it's just a single site, or if the entire study is really not supportive, we do not consider those data further.

Does that answer that question?

DR. LE: Yes, it does.

Do you want me to repeat my second question?

DR. MICHELE: Yes, please.

DR. LE: The second question I have is -- and I think this should conclude my line of questions here -- are there any policies in place -- let's say once you find a compliance issue, especially with forensic analysis that shows lack of integrity of the data, what are the policies and procedures that you have currently?

DR. MICHELE: Yes. So there are a number of policies and procedures for current contemporaneous trials. Again, the first thing we do is go out and

do a for-cause inspection, and whatever happens from there is taken one step at a time, and it depends on what was found during that audit.

Now, in this case, there were some questions that were raised about the data integrity of a couple of the studies from 55 years ago. I think at this point in time, it would be impossible to tell whether there truly were data integrities with those studies or not. All we were pointing out in our background package was that there is some evidence that perhaps the studies had some issues, but whether we can determine that there was an issue or there was not an issue 55 years ago, we certainly can't do that, and we're not impugning the integrity of those sites at any time.

DR. LE: Thank you.

DR. COYLE: Thank you.

I see one more question.

Dr. D'Agostino, please go ahead.

DR. D'AGOSTINO: Yes. This is Emma D'Agostino. My question is for the FDA, just going back to the bioavailability data again. I'm

wondering if you can comment that since the CHPA just talked about how we really don't know what the bioavailability is and that it's only 1 percent, or they're saying that we don't know that it's 1 percent, but we've heard from the FDA that we do think the bioavailability is only 1 percent, I'm wondering if you can comment on what we heard from the CHPA.

DR. MICHELE: Thank you for that question. So you're questioning the 1 percent bioavailability. I'm going to turn it over to Dr. Ren to answer that question.

DR. D'AGOSTINO: Thank you.

DR. REN: So about oral bioavailability, if you're talking about the strict definition of how many doses were absorbed in the human body following that oral, yes; other than that 38 percent flawed study, we do not have other good studies to support it. But it can be inferred because the parent phenylephrine drug concentration, the total AUC, or we can consider it as the amount, divided -- I'm talking about that

because it's in the blood, that's absorbed, and use that AUC value, or the amount value, divided by what was absorbed, the total phenylephrine, including metabolism, including parent, that's less than 1 percent. And the total, this phenylephrine absorbed, cannot be more than 100 percent of the dose that you intake, so therefore, the oral bioavailability for parent phenylephrine is less than 1 percent. That's why I said in the morning it's airtight; it's an inference.

Regarding those EC_{50} values from other drugs in other disease areas, I'm not an expert. We can go one drug by one drug and look at all these and have another meeting for this, but I'm not an expert in those areas. I haven't reviewed all these drugs. But in terms of alpha adrenergic receptor and agonist effect, I can say, based on the approved indication, which is for treating hypotension, if you compare that EC_{50} value to the blood or the plasma concentration of the parent phenylephrine, that's definitely higher than the EC_{50} value. So that's my answer for this question.

DR. D'AGOSTINO: Thank you.

DR. HOWARD: If the chair would allow Dr. Gelotte to add additional context?

DR. COYLE: Yes. Go ahead.

DR. HOWARD: Thank you.

DR. GELOTTE: Okay. We keep hearing about total phenylephrine, so I think the the best way to look at it -- oh, share; can we share --

DR. COYLE: Could I have you state your name for the record?

DR. GELOTTE: Cathy Gelotte.

DR. COYLE: Thank you.

DR. GELOTTE: Madam Chair, sorry.

DR. COYLE: No worries.

DR. GELOTTE: Alright.

I think what it comes down to is this total phenylephrine, and that's not the total. I mean, in general, the assays that were presented, the one that was presented from the briefing book with the the data from an NDA, that is really hydrolyzed from the sulfate. What's missing -- and like I said before, we've done metabolism studies, and the

only amount in the urine, which is a way to check how much was metabolized down that pathway, is 47 percent. So greater than 50 percent is getting in, and then once it's in, it goes through monoamine oxidase metabolism, and that's why we restrict that people cannot take this medicine on MAO inhibitors because it would increase their bioavailability of phenylephrine.

So what's happening here, it's a mixture. You have metabolites that prefer to stay in the plasma because the goal is to be eliminated in the urine. The free drug can leave the plasma and move to the site of action. So what you're measuring on total is really a mixture, which changes the overall pharmacokinetic profile, and you can see that with the red curve. It has a longer half-life, so it's not representation of the phenylephrine itself, and that's something that was brought up by one of the other committee members this morning, with Dr. Figg. Thank you.

DR. COYLE: Thank you.

Dr. Dykewicz, I'm going to give you the

floor.

DR. DYKEWICZ: Hi. Mark Dykewicz. So in our discussion, the comment's been made that the modern studies on seasonal allergic rhinitis patients that have not shown benefit with phenylephrine are not relevant to the consumer population to whom the phenylephrine products are indicated. But I look at the product label, and it says that oral phenylephrine products temporarily relieve nasal congestion due to the common cold, hay fever, or other respiratory allergies. So my reading of that would be that that would apply to patients with seasonal allergic rhinitis, which brings up the question in terms of patient usage and who is using this product.

I suspect it's a lot of patients with seasonal allergic rhinitis, but in the survey that was presented to the committee, starting around slide CO-8 and following, was there any effort made to determine, even with patient self-assessment, what sort of conditions were the people taking the oral decongestants for?

DR. HOWARD: I will ask Dr. Druce to approach.

DR. DRUCE: Howard Druce. I'd like to address the first part of Dr. Dykewicz's question. When you look at the guidelines for the evaluation of drugs for seasonal allergic rhinitis, you're looking at people who have got diagnosed allergic rhinitis for multiple years, positive skin tests, sustained nasal congestion in run-in periods and probably throughout the season.

You know, these people know who they are. They get symptoms in the spring, the fall, whenever, and they know who they are. If they get temporary nasal congestion and they follow the recommendations on the label of a phenylephrine box, they will take it for a short period of time, and then if it works for their nasal congestion, it satisfies their needs. If it does not, then clearly they will move to some form of other treatment.

But what I think we're dealing with here is probably with about 80 percent of studies, varied

epidemiologic studies, anywhere between 60 and 80 percent of patients with allergies don't reach the level of symptom complexity where they need to see a healthcare provider. They are perfectly well able to manage with the sort of medicine that you've heard Dr. Hendeles mentioned for their nasal itching and sneezing or Dr. Meltzer mentioned. But also, for this particular symptom, these are the sort of people who can use this.

The second point I'd like to make is that patients on the whole, who have allergies, don't say I have seasonal allergic rhinitis. People who have temporary stuffy noses know when they get it, when they get an upper respiratory virus, and they know when they do that, and that's almost everybody. They don't see a healthcare provider. And people with allergies who don't need to be treated throughout a season, again, know who they are and get short-term treatment.

I can't speak myself to this specific survey, but I think that the sort of people who are using this are not the same sort of people that are

being addressed in the practice parameters and the treatment guidelines.

DR. HOWARD: And while Mr. Tringale is approaching, I will at least add to the conversation that based on the sales data that we obtained while we were preparing for this meeting, the majority of the sales are actually occurring in cough-cold products that contain phenylephrine.

MR. TRINGALE: Mike Tringale, CHPA. Specifically with regard to the question about the survey, no, we did not screen for, nor ask about any condition that the respondent may have had.

DR. DYKEWICZ: Okay. Thank you.

Adjournment

DR. COYLE: Thank you.

So I don't see that we have any additional clarifying questions from the panel, so given that, we will now adjourn this first day of our two-day meeting. We've had lots of data presentations, and we will start promptly tomorrow at 9:00 am, September 12th. Panel members, as you individually consider the data that's presented, please do

remember that there should be no discussion of meeting topics with other panel members until we reconvene tomorrow. Day 1 is now adjourned. Thank you all.

(Whereupon, at 4:51 p.m., the meeting was adjourned.)