FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# NONPRESCRIPTION DRUGS ADVISORY COMMITTEE MEETING

# (NDAC)

Virtual Meeting

Day 2

Tuesday, September 12, 2023

9:00 a.m. to 11:57 a.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

P R O C E E D I N G S

(9:00 a.m.)

**Call to Order**

DR. COYLE: Good morning. 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 2 of the September 11th and 12th 2023 Nonprescription Drugs Advisory Committee to order. Dr. Jessica Seo is the 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'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and your affiliation. We'll begin by introducing the standing members of the NDAC, starting with Dr. Brittain.

DR. BRITTAIN: Good morning. I'm Kristy Brittain from the Medical University of South Carolina College of Pharmacy in Charleston, South Carolina, where I'm a professor, and I also serve as a clinical pharmacy specialist with MUSC Health, Charleston. Thank you.

DR. SEO: Thank you.

Next is Dr. Clement.

DR. CLEMENT: Yes. Stephen Clement, associate professor at two different universities, Inova Health System in Northern Virginia. I am a practicing endocrinologist.

DR. SEO: Thank you.

Next, we have Dr. Ginsburg.

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

DR. SEO: Thank you.

Next is Dr. King.

DR. KING: Good morning, Tonya King. I'm

professor of biostatistics at Penn State College of Medicine.

DR. SEO: Thank you.

And Dr. Pisarik?

DR. PISARIK: Paul Pisarik, family physician at Archwell Health in Tulsa, Oklahoma.

DR. SEO: Thank you.

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

DR. DATO: Good morning. Mark Dato, industry rep to NDAC and retired pediatric pulmonary. Thank you.

DR. SEO: Thank you.

We'll go on now to our temporary voting members, and first we have Dr. Amirshahi.

DR. AMIRSHAHI: Hi. Maryann Amirshahi. I'm an emergency medicine physician and professor of emergency medicine at Georgetown University School of Medicine. I'm a medical toxicologist for the National Capital Poison Center and a clinical pharmacologist.

DR. SEO: Thank you.

Next, we have Dr. Blalock.

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

DR. SEO: Thank you.

And Dr. Coyle?

DR. COYLE: Good morning. Maria Coyle. I'm an associate professor at the College of Pharmacy at the Ohio State University in Columbus, Ohio. I'm also a clinical pharmacy specialist over at our Wexner Medical Center, practicing in ambulatory care.

DR. SEO: Thank you.

And Dr. D'Agostino?

DR. D'AGOSTINO: Good morning. Emma D'Agostino, an advocate with the Cystic Fibrosis Foundation and a medical writer, and I have a background in biochemistry.

DR. SEO: Thank you.

And Dr. Dykewicz?

DR. DYKEWICZ: Good morning. I'm Mark

Dykewicz. I'm an allergist-immunologist. I'm at Saint Louis University School of Medicine, where I'm chief of allergy and immunology and professor of internal medicine.

DR. SEO: Thank you.

Next is Dr. Figg.

DR. FIGG: Hi. William Figg, clinical pharmacologist and investigator at the National Cancer Institute, NIH.

DR. SEO: Thank you.

And Dr. Jones?

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

DR. SEO: Thank you.

And next is Dr. Kim.

DR. KIM: Good morning. I'm Colonel Esther Kim. I am an otolaryngologist with a subspecialty training in rhinology. I'm stationed at Fort

Belvoir at the Augusta T. Medical Center.

DR. SEO: Thank you.

And Dr. Le?

DR. LE: Good morning, everyone. I'm Jennifer Le. I am professor of clinical pharmacy at the UC San Diego Skaggs School of Pharmacy, and my area of specialty is pediatric infectious diseases and clinical pharmacology.

DR. SEO: Thank you.

And Ms. Schwartzott?

MS. SCHWARTZOTT: I am Jennifer Schwartzott, and I am your patient representative.

DR. SEO: Thank you.

We'll now introduce our FDA participants, and we'll begin with Dr. Michele.

(No response.)

DR. SEO: Dr. Michele, I'm sorry to interrupt. The audio might be muted. Can we check the audio in the conference room, please?

DR. MICHELE: Can you hear me now?

DR. SEO: Yes. You're coming through loud and clear. Thank you.

DR. MICHELE: Very good.

Good morning, everyone. I'm Theresa Michele. I am the director of the Office of Nonprescription Drugs, and I am a practicing pulmonary critical care physician.

DR. SEO: Thank you.

Next, we have Dr. Todd.

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

DR. SEO: Thank you.

And next is Dr. Lenhart.

DR. LENHART: Good morning. I'm Martha Lenhart, the deputy director of the Division of Nonprescription Drugs I in the Office of Nonprescription Drugs. Thank you.

DR. SEO: Thank you.

And we have Dr. Adah.

DR. ADAH: Good morning. Steven Adah, associate director for monographs, Division of Nonprescription Drugs I. Thank you.

DR. SEO: Thank you.

Next is Dr. Starke.

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

DR. SEO: Thank you.

And Dr. Bishop.

LCDR BISHOP: Good morning. I am Dr. Ben Bishop, pharmacist and reviewer in the Division of Nonprescription Drugs I.

DR. SEO: Thank you.

We also have Dr. Ren.

DR. REN: Good morning. This is Yunzhao Ren, the acting team leader of Division for Inflammation and Immune Pharmacology in the Office of Clinical Pharmacology, FDA.

DR. SEO: Thank you.

And finally, Dr. Pham.

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

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

DR. COYLE: Thank you.

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 the meeting.

We are aware that the 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. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Seo, could we go back and ask Dr. Calis to introduce himself into the record? I think we might have missed him.

DR. SEO: I am so sorry. I apologize for that.

Dr. Calis, if you could please state your name and introduce yourself into the record.

DR. CALIS: Yes. Good morning. I'm Karim Calis. I am a senior scientist at the NIH in Bethesda, Maryland, where I work as director of Clinical Research and Compliance for the National Institute of Child Health and Human Development, and I'm also chair of the NIH IRB in the Office of Intramural Research. Thank you.

DR. SEO: Thank you so much, Dr. Calis, and back to you, Dr. Coyle.

DR. COYLE: Thank you.

We will now proceed with the summary and

introduction to discussion, followed by the charge to the committee from Dr. Martha Lenhart.

**Summary and Introduction to Discussion**

**Martha Lenhart**

DR. LENHART: Good morning, and welcome to Day 2 of our meeting. I'm Martha Lenhart, the deputy director, Division of Nonprescription I. As noted yesterday, the main objective of this meeting is to consider the efficacy of oral phenylephrine as a nasal decongestant, particularly the phenylephrine data that has become available since the committee last considered this topic in 2007.

With the availability of new studies since FDA last evaluated oral phenylephrine under the cough-and-cold monograph, the agency undertook a careful and thorough review of all the available data. We are asking you to help us think critically about the data, and what those data may or may not show.

Phenylephrine is one of two orally administered alpha-1 adrenergic receptor agonists that were recognized as GRASE in the Cough-Cold

Monograph published in 1994. Phenylephrine is also GRASE for direct intranasal and topical uses. This meeting is focused specifically on the use of orally administered phenylephrine as a nasal decongestant. The indication of oral phenylephrine is the temporary relief of nasal congestion regardless of etiology. The monographed dose for adolescents and adults is 10 milligrams every 4 hours, not to exceed 60 milligrams in 24 hours.

The regulatory standard for effectiveness of monographed drugs from the Code of Federal Regulations state that effectiveness means a reasonable expectation in a significant portion of the target population that the pharmacological effect of the drug will provide clinically significant relief of the type claimed. Further, proof of effectiveness shall consist of controlled clinical investigations.

Let's now review the 2007 NDAC meeting. It was convened to discuss the safety and effectiveness of oral phenylephrine as a nasal decongestant because of additional data that had

become available since FDA's GRASE finding for phenylephrine in 1994. At the meeting in 2007, the committee also considered the original studies supporting effectiveness for oral phenylephrine.

The committee noted that results were not consistent across studies in terms of nasal airway resistance and agreed that symptoms should be the essential primary endpoint for efficacy studies of congestion. The committee also noted that evidence of efficacy consisted primarily of studies conducted decades earlier and on limited numbers of subjects, and due in part to the small size of the studies, that nasal airway resistance results may not be generalizable to a wide population.

For clarification, three voting questions were posed at the 2007 NDAC. For the first voting question, the advisory committee disagreed with the statement that phenylephrine in a 10-milligram, immediate-release formulation has been shown to be effective when dosed every 4 hours for the symptomatic treatment of nasal congestion, and that no additional studies are needed to support its

effectiveness. In other words, did it meet GRASE standards? Two voted yes; ten voted no.

The second question was worded, given the available data that exist, the evidence is supportive that the 10-milligram, immediate-release formulation may be effective. Eleven voted yes, one voted no. And the third question asked whether additional studies are needed to assess the efficacy and safety of higher doses. Nine voted yes; three voted no.

In conclusion, the committee recommended that additional trials be conducted, specifically multicenter, parallel, randomized, blinded, placebo-controlled trials, preferably with an active control, to evaluate nasal congestion scores and symptom relief. In the years since the 2007 NDAC, more data have become available.

Certain clinical pharmacology information presented yesterday by Dr. Ren was not available to the 1970s DESI panel. This includes that only parent phenylephrine with its metabolites is active. We note discussion yesterday about the

bioavailability of phenylephrine. Due to the extensive first-pass mechanism, only a fraction of the orally administered dose is present as parent phenylephrine in the systemic circulation. The $C_{max}$ value of parent phenylephrine following an oral dose of 10 milligrams is low, about 1 nanogram per mL. One nanogram per mL is approximately one-third of the in vitro alpha-1 adrenergic $EC_{50}$ value.

Because the blood vessel is the target organ and the site of action for parent phenylephrine, the plasma concentration of parent phenylephrine is clinically relevant. This peak plasma concentration is unlikely to achieve a pharmacologic effect in the nasal mucosa needed for nasal decongestant. Both the PK and PD data suggests that a much higher dose of oral phenylephrine may be needed to achieve a nasal decongestant effect.

Original data that supported the GRASE determination, along with new data, were reviewed and presented by Dr. Starke. The original efficacy studies conducted prior to the 2007 NDAC do not

meet today's trial design standards. For example, clinical and statistical methodology issues of these studies included small study sizes that limit generalizability and inconsistent results across early studies, suggesting possible data integrity issues, and of primary importance, the use of unvalidated nasal airway resistance, or NAR, for efficacy assessments. In contrast to NAR, nasal symptoms scores are the gold standard as an endpoint because they directly measure the symptom of interest. Every drug approved over the past 30 years in the cough, cold, allergy space has demonstrated to be effective based on nasal symptoms scores.

Studies conducted after the DESI panel review and presented at the 2007 NDAC consisted of single-center, proof-of-concept studies. For these studies, nasal congestion score results showed that a 10-milligram oral phenylephrine dose was not significantly different from placebo. More recent studies consisting of multicenter, parallel, randomized, blinded, placebo-controlled trials also

showed that a 10-milligram dose of phenylephrine was not significantly different from placebo. In summary, the new data appear compelling that the monographed dose of oral phenylephrine results in no meaningful systemic exposure and no evidence of efficacy.

**Charge to the Advisory Committee - Martha Lenhart**

DR. LENHART: At this time, let's move to the charge to the advisory committee. These are the questions we ask you, the advisory committee, to discuss and vote upon. There are three discussion questions and one voting question. We note that the questions are reframed from those of the briefing document and are provided as a final questions document in the meeting materials. We ask you to focus on the data during your discussions rather than on a regulatory decision. I will present the questions sequentially in the following slides.

The first question is a discussion question. Discuss the current scientific efficacy and pharmacokinetic data for phenylephrine. For this

question, we are asking you to discuss the data available to the 2007 NDAC and beyond. The second question is a voting question. You are asked to provide a yes or no response to the question, do the current scientific data that were presented support that the monographed dosage of orally administered phenylephrine is effective as a nasal decongestant? Base your response on the efficacy standard noted by Dr. Michele yesterday and provided in the slides today.

If you respond in the affirmative, please discuss what data you consider supportive. Identify specific studies that you find supportive and why those studies are supportive. If your vote is no, please discuss what additional data, if any, are needed to assess phenylephrine pharmacokinetics or efficacy.

The third question, a discussion question, asks you to discuss whether the current scientific data that were presented support that a dose of orally administered phenylephrine higher than the monographed dosage would be safe and effective. We

are interested in discussion of higher than the monographed dose for adolescents and adults of 10 milligrams every 4 hours, not to exceed 60 milligrams in 24 hours. For the last question, a discussion question, we are asking you to discuss the implications for and communication strategies to consumers regarding the current oral phenylephrine data.

In closing, thank you for your thoughtful consideration of these questions, and now I'll return the floor to Dr. Coyle.

DR. COYLE: Thank you, Dr. Lenhart.

DR. LENHART: Thank you.

**Questions to the Committee and Discussion**

DR. COYLE: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will proceed with the questions to the committee and the panel discussion. I would like to remind public observers that while this meeting is open for public observation, public attendees may not

participate except at the specific request of the panel.

After I read each question, we will pause first for any questions or comments concerning its wording, and then we will open the question to discussion itself. And I would just like to encourage all of our members, including the non-voting members of the advisory committee, to participate in this discussion and to share your expertise so that we can have a very well-rounded and robust discussion of the issues at hand today.

So let's proceed to our first question, which is a discussion question. Question 1, again, we're going to first just focus on the wording and be sure that it's clear, discuss the current scientific efficacy and pharmacokinetic data for phenylephrine.

Are there any concerns or clarifications needed on the question itself?

(No response.)

DR. COYLE: If there are no questions or comments concerning the wording of the question, I

will now open the question to discussion.

Dr. Figg, please go ahead.

DR. FIGG: Sure. Two points to be made on the pharmacokinetics. First, the 30 percent that was originally reported is not because of, really, the assay, but it's really because it was measuring the isotope. So a metabolite that still has the isotope was being measured, so that has nothing to do with what was the parent concentration in the systemic circulation.

Second, there was a lot of trying to confuse things yesterday, in my opinion, for CHPA's discussion about metabolites. First-pass metabolism does not result in the parent drug being in the systemic circulation, and bioavailability is really only the parent drug in the circulation, so that 1 percent is accurate or close to it. So both of those points suggest the concentration of phenylephrine being achieved in the circulation is substantially low.

DR. COYLE: Thank you, Dr. Figg.

I'll go ahead and call on Dr. Dato. Again,

please state your name for the record.

DR. DATO: Hi. Mark Dato. Yesterday, at least my understanding, there seemed to be a distinction being drawn in the study populations between common cold and allergic rhinitis, and I don't know if it's possible at this time, but Dr. Druce seemed to be dismissing the population of the 2007 and post-studies based on allergic rhinitis versus common cold, which were the majority of pre-2007.

I'm just curious if he could comment on why he feels those populations, one, are different, and two, why the post-2007 shouldn't be considered.

DR. COYLE: CHPA, is Dr. Druce available?

DR. HOWARD: He is. I'll ask him to approach, and may we have him approach now? Okay.

DR. DRUCE: Thank you. Howard Druce. In response to the question, there are both similarities and differences between common cold and allergic rhinitis. There was a presentation yesterday of the pathophysiology, and you saw that there's a different pathophysiology but a

commonality with the blood vessels and the mechanism of congestion and decongestion, and you heard Dr. Meltzer from the public presentation expressing the same sentiment.

Most of the studies that were supporting the pre-2007 studies were in the common cold model, and they were extrapolated because of this commonality to allergic rhinitis because of the common vasculature and the common mechanism there. But admittedly, most of the data is in the common cold, and the strength of the data is based there.

The newer studies do not mirror the earlier studies in the sense that they are looking at a different population of people. They're looking at people who have sustained nasal congestion. They're looking at people who have year-on-year repetitive seasonal symptoms and not the temporary type of nasal congestion that can happen in that condition but can also happen independently, which is where people don't end up seeing healthcare practitioners.

So summarizing all of that, all the new

studies do not address, at least in my mind, the question of efficacy of phenylephrine for temporary relief of nasal congestion, and therefore it would not be expected that they would necessarily answer that question, and so the bulk of the data is in the common cold model. Thank you.

DR. DATO: Thank you.

DR. HOWARD: And I would like to to add that I know we talked a lot yesterday about the various treatment options, but just so that we're all clear, there is no oral treatment option besides phenylephrine that provides temporary relief that is available OTC without restriction. So that means that only pseudo would be available, but that's restricted behind the counter.

And it matters because, like for me, I live in West Virginia, and there's no local pharmacy in my hometown, so if I needed something with pseudoephedrine, I'd have to drive to the next town over. And when we think about the alternatives, the oral and the intranasal antihistamines, they treat allergic rhinitis, but they're not indicated

for temporary relief of nasal congestion due to the common cold. And the intranasal decongestants do provide temporary relief for allergic rhinitis and common cold, but consumers prefer --

DR. COYLE: I'm going to interrupt slightly because this isn't really relevant to the question that was asked by Dr. Dato. So that may come up later by one of the panel members, but for now I'd like to invite FDA to respond to the same question that Dr. Druce responded to in terms of the study population for the newer studies. Thank you.

DR. MICHELE: Thank you, Dr. Coyle, and thank you, Dr. Druce [sic - Dato], for that question. This is Teresa Michele, Nonprescription Drugs at FDA. I want to go back to the indication for phenylephrine. The indication for phenylephrine is for the temporary relief of nasal congestion regardless of indication, so it covers both the allergic rhinitis indication, as well as the common cold indication. And as we heard yesterday, the physiology of the nasal congestion is the same for both indications.

So this is a very broad indication, and the studies that were conducted more recently, the placebo-controlled trials that were presented from both Merck and Johnson & Johnson, as well as the environmental exposure chambers, were designed to support the same indication that is currently for phenylephrine, so we do believe that those studies are relevant. Thank you.

DR. COYLE: Thank you, Dr. Michele.

Dr. Dykewicz, please go ahead.

DR. DYKEWICZ: Two points. I do believe that the studies looking at seasonal allergic rhinitis are pertinent to looking at the indication, as just stated by the FDA, and I find it difficult to consider, or to conceive the idea, that there would be substantial improvement in congestion with the common cold when we're seeing lack of efficacy in seasonal allergic rhinitis.

The other thing is just lest we forget, although most of the more modern studies have been in allergic rhinitis, we do have the Johnson & Johnson cold trial that had an enrollment

of 193 subjects -- and for members of the committee, that would be back on the FDA slides 70 and following -- and that study failed to show any improvement in congestion scores in the setting of a common cold.

So I think the data with that is consistent with the allergic rhinitis data and demonstrates that modern studies well conducted are not showing any improvement in nasal congestion with phenylephrine. Thank you.

DR. COYLE: Thank you, Dr. Dykewicz.

Dr. Le, go ahead, please.

DR. LE: Hi. Jennifer Le from UC San Diego. I just wanted to thank Dr. Figg for confirming the bioavailability of oral phenylephrine because I think what the data presented yesterday was kind of confusing, especially if you're not coming from a clinical pharmacology background, so thank you for that.

I do want to also add on the pharmacology side the comments about volume of distribution; that since it's very high, the assumption would be

it goes into pretty much all the tissues. While that may be true, the consideration that we have here is really whether or not it goes into the nasal mucosa for the site of action. My thoughts are without adequate data to support that, I don't think we can make the assumption that it's going to the site of action, and I wanted to see if CHPA has comments on that, as well as the FDA.

DR. HOWARD: Just a moment.

We'll ask you to repeat the question, as Dr. Gelotte is approaching the podium, and then if Dr. Druce has anything to add, he'll also be able to.

DR. LE: Sure. My question was on surrounding the volume distribution, and this was brought up by Dr. Gelotte yesterday in terms of since it has a high distribution, the assumption would be it goes into many tissues. But I think the question we have is whether or not it gets to the site of action for the indication, which is the nasal mucosa. And my belief is that if we don't have real data to support that it actually gets

there, we cannot make that assumption that it does.

DR. GELOTTE: Okay. The data that we brought up yesterday for you, it was in the core presentation where we showed the pharmacokinetic curve with an array of the nasal airway resistant curves. Now, those are physiological responses to the drug in the nasal mucosa, so it does distribute there, and that's where you get -- can I share a slide?

DR. COYLE: Yes. Which slide?

DR. GELOTTE: Oh, thank you.

Yes. So this was the one we were speaking about yesterday, where you see the pharmacokinetic curve in the plasma on the left, and then you see the nasal airway resistance, which is a physiological response in the nose and increasing air flow. So this is indirect evidence because we don't actually measure in the tissues, but it needs to get into the tissues in order to have this pharmacodynamic response in the nasal mucosa. So this is the indirect evidence that the drug gets to the site of action.

DR. LE: Thank you for that. I'd like to get some comment from the FDA, if possible.

DR. GELOTTE: Thank you.

DR. COYLE: Yes, I'll recognize, Pham, who has their hand up as well.

Dr. Pham -- or Dr. Ren. I apologize.

DR. REN: Hello. This is Yunzhao Ren. Hello? Can you hear me?

DR. COYLE: Yes.

DR. REN: Hi. This is Yunzhao Ren again. So yes, we agree that currently there's no data available directly measuring the phenylephrine concentration in the nasal mucosa, and we also agree that because there is lack of evidence, that the nasal mucosa can enrich the phenylephrine concentration locally. So therefore, it's likely the phenylephrine concentration in the nasal mucosa, in the blood vessel of the nasal mucosa, is probably the same concentration in the plasma or in the blood, and it's lower than the in vitro $EC_{50}$ values.

DR. LE: Thank you.

DR. COYLE: Dr. Le, did that address your question or would you like additional information from someone else?

DR. LE: I think that addresses it. Thank you.

DR. COYLE: Okay. Great. Thank you.

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

DR. CLEMENT: Yes. Thank you very much. Steve Clement. As I mentioned yesterday, I'm learning like crazy on this. Obviously, I don't see these patients personally in my current field but I do work with pulmonologists and allergists, and actually one of my closest colleagues is an ENT at George Washington. So without giving him data about the study, I asked him, "What does the nasal mucosa look like?" I'm very visual, so I want to talk to people that actually see this every day, and he looks at the nasal mucosa every day in his patients.

His comment -- and we have one of the committee members as an ENT as well, and I'll be

interested in her feedback -- is that when you look at engorged septa and engorged mucosa in the nose, it looks the same, whether it's allergic rhinitis or a cold. He cannot see a difference on that. There may be difference in goblet cells, and mast cells, or whatever in terms of histology, but when they're looking at it, it looks exactly the same.

So I was really concerned about this big argument, that could we be missing something or not having really solid data on the common cold, but from actually physically looking at it, which is a little bit of a crude measurement, it looks exactly the same. When I just historically look at the data on pseudoephedrine, pseudoephedrine worked, and it worked regardless of whether it was common cold or seasonal allergic rhinitis.

So the argument that these are different diseases I sort of pushed back a little bit, at least from the data that I'm looking at, is that there are more similarities than differences in terms of the pathophysiology, the engorgement of the mucosa and the cause of the airway obstruction.

That's all leading up to the issue -- well, first I'll go back to the beginning. I think the older data is completely not credible. That was my first comment. The PK data is very compelling thanks to the work of the FDA and their discussions, that it's less than 1 percent. So if you get less than 1 percent, it really explains a lot of the negative data right off the top.

The Merck data was incredibly compelling, is that they showed no signal at all, not even a tinge of a signal up to 40 milligrams, which is 4 times the current available dose, and in multiple studies, in their dose-finding study, and also in their 30 milligrams ER 2011 study, no signal, none, zero.

The last one, the J&J study, it would be great, if we had a perfect world, to have a completely done study in the cold, particularly if they had an active control such as pseudoephedrine, which we don't have. So if we had a perfect world and unlimited resources, it would be great to see that study done with all those things to really

look a little bit closer at the common cold, but given that we don't have incredible unlimited resources, we do have PK data that shows that this is probably going to be a futile study to begin with. I think we have enough already. I don't think we need any additional data, and I'll conclude my comments with that. Thank you very much.

DR. COYLE: Thank you.

So I'm going to recognize myself here at this moment. Maria Coyle. I have two questions, and I'd like to direct them, really, to my fellow advisory committee members first, and then if more information is needed, maybe we'll call on some other experts.

My first question really goes to this point of efficacy versus effectiveness in the real world. I would be curious from my colleagues here on this call, who do work with patients who have nasal congestion, either as part of an allergic rhinitis or some other syndrome, what would you consider to be an effective resolution of symptoms or

improvement in symptoms?

I think we heard both from the FDA and from CHPA that it's difficult to quantify how much nasal airway resistance change is discernible or worth it to a patient, or even how much a change in the nasal congestion scores are worth it to a patient. So I would be curious as to what you would view as an effective treatment for nasal congestion, and if someone could speak to that from our committee.

Dr. Le, your name hand is up. Please go ahead.

DR. LE: Sure. Actually, I'm speaking from my own son who has asthma, and he has really bad nasal congestion for months now. And the only thing that really works for him when we need it would be what was mentioned yesterday, inhaled corticosteroid with inhaled Astepro. Once, I believe, he was given oral pseudoephedrine, but phenylephrine never really worked for him.

DR. COYLE: Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: Well, I could respond to that

in several different ways, and I guess I first of all would say, because I am an allergist-immunologist, I am seeing people who have not done well, or they failed to benefit from treatments that they have obtained over the counter. Of course, in the whole big perspective these days, that includes not only over-the-counter phenylephrine; some patients have taken behind-the-counter pseudoephedrine, nasal corticosteroids, and so forth.

So I think oftentimes when a patient comes into the office, I'm getting a global report from the patient, not necessarily in quantitative terms, but just, "This is not giving me the relief I need with nasal congestion. I'm having difficulty sleeping at night. I'm having difficulty functioning during the day." And you can administer to patients some scoring system, some questionnaires, and that you can get a quantitative sense about this, but I think in general practice, it's kind of a global sense from the patient about whether they feel it's enough benefit to them

That being said, there is a big placebo effect in treatment of rhinitis. For instance, it's not uncommon that you'll see 30 percent improvement with placebo in many patients. So the fact that some patients think that they are getting relief from specifically oral phenylephrine can be a placebo effect, and I think our role, not just from a regulatory standpoint but also healthcare providers, is to make recommendations to patients that will give them the best benefit for relief of their symptoms. And that would be my approach as to the question about whether oral phenylephrine is giving the benefits that they need beyond placebo.

DR. COYLE: Thank you.

Then I have one follow-up question to you, Dr. Dykewicz. If you have a patient with significant symptoms, would you be inclined to direct them over the counter or would you be more inclined to provide some sort of a prescription decongestant? And maybe that depends, but --

DR. DYKEWICZ: It very much depends on the patient. I would say, typically, by the time a

patient is coming, and suffering, into my office, I'm not simply recommending, let's say for allergic rhinitis, that they get behind-the-counter pseudoephedrine, which we know has established efficacy, but depending on the severity of the symptoms, how frequently they're having symptoms, I would be recommending nasal preparations.

I do recognize that patients would prefer to have oral agents if they could, but if you look at the relative effectiveness of the nasal preparations that are available, and I'm talking short-term nasal decongestants, nasal corticosteroids, which are available over the counter, and intranasal antihistamines that are available over the counter, those are all the options that I would give, depending on the severity of the patient, to a patient to get them the relief that they need.

DR. COYLE: Thank you.

I'd like to recognize Dr. Kim. Please go ahead.

DR. KIM: Good morning. I guess on the

panel, I'm the only otolaryngologist giving my perspective. When we evaluate patients who have nasal congestion, we're going to look at them in a way that may warrant some sort of surgical intervention, and a lot of times we're seeing these patients after they've tried basically everything to help them with their obstruction; however, we still have to go through our due diligence to make sure that they've at least tried the medications for a period of time before we determine if they failed or not.

I do want to point out that the way we evaluate our patients is that we are going to be looking at the lining of their nose, the size of their turbinates, position of their septum, and we also evaluate their nasal valve. So when we look at that in its entirety, we look at nasal obstruction as being very multifactorial. With regards to medications, I will say that the vast majority of my patients probably have already tried the over-the-counter preparations that are available but, in general, the way maybe an

otolaryngologist would look at their medical management is if they have been on topical corticosteroids, topical antihistamines, and would be our basis and our standards of care to see if their medical management was sufficient.

I would say that from the standpoint of the way I understand phenylephrine, because this is going to work on the alpha adrenergic as an agonist, for the most part, we look at the turbinates as really being the only vascular structure that is reversible inside the nose. Now, there is some argument that maybe there are some swell bodies in the nasal cavity, such as the swell bodies on the septum or on the floor of the nose, but those in general are probably not consistent across patients. It's just really mainly the action on the inferior turbinates.

So again, this becomes a little bit of a confounder because you have the other structures in the nose that can contribute to the nasal obstruction, but by and large, the inferior turbinates, which is going to be mainly what's

being targeted by phenylephrine, I will say that this is not a common medication that I will be reviewing because we don't feel that that is a sufficient medication that is going to affect the turbinates.

Then there is data that I'm reviewing here, where a lot of it is reviewing the nasal airway resistance and, again, when I look at the nasal cavity, there are so many other factors that can go into that determination. If there was a significant improvement with the phenylephrine, we would see sort of marked reductions in that nasal airway resistance, but at the end of the day don't really have a significant improvement, is basically how I have seen a lot of the studies. You know, at best, you may have 60 minutes of improvement, but if the medication is being dosed every 4 hours, then perhaps for 3 hours you're still sort of suffering and not getting any benefit.

DR. COYLE: Thank you, Dr. Kim. I have a follow-up question. I'm paraphrasing a little bit, so please tell me if I'm understanding this

accurately. It sounds like from what you were saying, that a patient coming with a clinical history of using an over-the-counter or prescription nasal steroid or nasal antihistamine might provide some clinically useful information, but a patient taking oral phenylephrine might not provide a lot of clinically useful information for you in deciding --

DR. KIM: That's right.

DR. COYLE: Okay.

DR. KIM: That's right. That's certainly not part of my personal evaluation of patients. The way, I would say, the majority of our data would demonstrate the effective medicines that we would prescribe our patients on whether or not we have reversible nasal obstruction is going to be the usage [indiscernible] of the intranasal corticosteroids plus or minus the intranasal antihistamines.

Again, this is going to be more on the allergic rhinitis thing; I recognize that. I know there was a lot of discussion about having an

actual cold. We probably would not be prescribing topical antihistamines in somebody who is presenting with an acute upper respiratory infection causing some nasal obstruction. So I do want to just make sure that that is clear, that this is really more in the setting of a patient coming in with really more chronic symptoms, which we would designate as patients having symptoms for greater than 6-to-10 weeks or so.

DR. COYLE: Thank you. Thank you, Dr. Kim, and I appreciate that context; very important.

Dr. Jones, please go ahead.

DR. JONES: Yes. I just wanted to give perspective also from the pediatric side. I mainly see children as an allergist, so I mainly see children with allergies. So just thinking about what's meaningful to patients and to families in pediatrics, we always want to have objective measures that we can assess in clinical trials, but at the end of the day, the thing that is most meaningful are the symptoms that the patients are experiencing and how they're able to go along with

their daily activities.

In children, the things that come up are related to congestion; or allergic rhinitis; or interfering with sleep; interfering with being able to eat; interfering with not being able to participate in normal activities like sports and exercise; and also having this mouth breathing, which a lot of kids don't like to be mouth breathers for many reasons. They might get teased at school and that type of thing. So those are the things that I talk about with my patients.

I think in the studies that were conducted, the early studies looking at the nasal resistance scores, there are a lot of questions about those studies of how reliable those objective assessments were. So I think certainly if you're doing objective assessments, they need to be reliable across studies and across operators, but they also need to align with the clinical symptoms. I think with the newer studies that were done after 2007, using what's currently the gold standard of symptom scores, we don't see efficacy. I believe that

data. I think it's impactful and that we should listen to that data.

I think also this discussion about allergic rhinitis congestion versus common cold congestion, in these later studies, they looked at patients with seasonal allergic rhinitis, and that may not be that different from congestion from a common cold because seasonal allergic rhinitis will often fluctuate with the pollen counts or the allergen counts in the air. Currently, today in Kansas City, our ragweed pollen counts are very low. Yesterday, we had rain and the weather has kind of changed, where last week the pollen counts were really high. So patients will experience fluctuations in their symptoms depending on the environmental exposure. Sometimes those symptoms may be more short-lived and may be more similar to what you might experience with a common cold.

So I do believe that congestion is likely very much the same across allergic rhinitis versus the common cold, and I certainly believe for a medication to be effective is that it has to

actually get to the site of action. It has to get to the microvasculature in the nasal mucosa. So I think the other point in regards to the bioavailability, if the concentrations of the parent compound are so low in the systemic circulation, where your total exposure is so low, even if it does make it to the nasal mucosa, the concentrations are so low there, it's not likely to have significant action to ameliorate symptoms.

So those are my primary thoughts, and again just kind of from the perspective of pediatrics and what I think is important for patients.

DR. COYLE: Thank you, Dr. Jones.

If I were to do a short summary of what we have discussed to this point, I think several panel members have mentioned that they do believe that the concentration of parent drug that is actually reaching the tissue in the nasal passages is low; that overall, the later studies do seem to provide some strong evidence that the phenylephrine at 10 milligrams may not be effective and is likely not effective in relieving nasal congestion, at

least in the populations studied; that there seems to be some agreement that the populations of patients with seasonal or allergic rhinitis and those patients with cold symptoms may overlap, so not an unreasonable study population for those later trials, as well as some clinical context around what might be considered an effective treatment and how that effectiveness might be assessed.

That is I think what we've discussed so far. I do see that, Ms. Schwartzott, you have your hand up. I'd like to acknowledge you with the floor.

MS. SCHWARTZOTT: It appears that we're all in agreement that phenylephrine is not effective, so that, to me -- and again, I'm not a doctor, but I am a patient who has had colds like all of us have, and I've taken the over-the-counter things that haven't worked.

I want to question if this brings up a safety concern, and I think that's very important because safety is even more important than the efficacy. Phenylephrine on its own, if you take

it, you don't really have any severe adverse events, but how about the adverse event, that if you're taking something that's not effective, a lot of people will continue to get sicker. They're having the mild cold symptoms, so they take the drugs, and they don't work, so they end up developing further symptoms, and it keeps traveling, getting worse and getting worse, and you can end up with some severe health issues.

That actually happened to me. In 2021, I had rhinovirus. It started out very mild, and within 3 or 4 days, I was in the ICU with pneumonia and hooked up to breathing machines because I couldn't breathe on my own, and that was the only thing they could find wrong with me, was the rhinovirus. I had gone, on the day that I was starting to feel somewhat lousy, to CVS and picked up one of those packages of cold things. I don't remember exactly what it was, but I know it wasn't pseudoephedrine because I cannot take that. I was already on allergy medication. Having no allergy symptoms at all was perfectly fine until I was

exposed by my friend who was sick.

So not everybody gets better from the cold. It can progress. It can get really, really severe, and I think that we need to question it's not just the efficacy; it's the safety aspect of these people need treatment, and they're not getting the treatment if the drug is not effective. So I'd like to hear what the specialists have to say about that.

DR. COYLE: Thank you, Ms. Schwartzott.

Is there anyone on the panel that could respond to her question, particularly with specialty in this area? I think if I'm rephrasing, the question would be specifically the lack of treatment and the risks associated with lack of treatment with an effective decongestant, and how that might play into our considerations.

Yes. Dr. Dykewicz.

DR. DYKEWICZ: Actually, this is a very important question. In practice, the major potential complication of uncontrolled nasal obstruction might be the development of bacterial

sinus infections. That doesn't happen very often, but if you are looking at trying to maintain the patency or the openness between the inside of the nose and the sinus cavities to avoid mucus accumulation and possible development of a bacterial sinus infection, you certainly would want to achieve that or try to achieve that with an effective treatment, and oral phenylephrine's not going to do it.

There would be alternatives such as intranasal decongestant sprays that for short term might work better. It would be off label. One might consider a nasal corticosteroid to help reduce congestion swelling within the nose. But I think, are there clear-cut studies that would prove that some of these alternative treatments are reducing the risk of developing bacterial sinusitis with the need for antibiotics and potential other complications? We don't have studies that clearly demonstrate that.

DR. COYLE: Thank you.

Dr. Jones, could you comment?

DR. JONES: Yes. I think that brings up a really important point in that the risk of taking a medication that's not effective for a particular condition, I think anytime you introduce a molecule into the body and it's not achieving effect or addressing the condition that it's meant to address, there's risk in that. There could be risk of allergic reaction or risk of anything else that involves introducing a foreign molecule into the body.

I think the other thing for me that's also concerning, there's been some discussion about patients who live in rural or underserved areas, and not able to access pseudoephedrine or other medications. I think there's an additional risk for these patients as well. If all that they may have access to is a medication that's not effective, I think that additionally harms these patients. So the real fix is providing access for these patients and not necessarily providing a medication that has been shown to be ineffective.

DR. COYLE: Thank you.

I'm going to acknowledge Dr. Le.

DR. LE: I think a very, very important point has been brought up in terms of patient safety. I've sat on the FDA and also AHRQ for four years now, and I wear different hats depending on what meeting I'm going to. So with the FDA, you kind of separate efficacy from safety because it's related to the drug, usually, drug efficacy and drug safety, and there are different studies to evaluate that. But on AHRQ, patient safety is really the number one priority for us, and within that patient safety, one aspect of patient safety is if the drug works and if there are appropriate diagnostics for the indication. And here, when the drug doesn't work, it is a patient safety issue for us, outside of the drug adverse drug effects as well.

So I think that should be considered bias in terms of, well, if we see with the most recent data -- and they are RCTs, randomized-controlled trials, double-blind and stuff, and there's more than one. So there's definitely enough efficacy

data for us to see that, like oral epinephrine, at the current dose, it's unlikely to work, then patient safety is an issue, and I think the committee members should consider that.

DR. COYLE: Thank you. Thank you, Dr. Le.

Dr. Brittain, please go ahead.

DR. BRITTAIN: Hi. Dr. Kristy Brittain. I just wanted to make mention, because I haven't really heard some discussion about it thus far, but I think the other important component when we're thinking about safety is just to remember that phenylephrine over the counter is most often in combination with other products. So yes, it's a single-entity product, but I would garner to guess that most of the products that are being purchased are products that have multiple other ingredients in them.

So I think it's just an important consideration to think; that our population that's using these are potentially getting exposure to other things as well. And again, going back to the discussion about access, I think we've talked about

there are a lot of other options that are still over the counter that that don't include phenylephrine, so I just wanted to make that note.

DR. COYLE: Dr. Brittain, can I ask a follow-up question? Is there a particular concern that you have in terms of this being part of a combination product? Could you envision a scenario or give us an example of how you might see that influencing patient outcome?

DR. BRITTAIN: I mean, I think the biggest is we've talked about the dose effect thus far, so since we have this kind of subtherapeutic dose, and there's a potential that individuals will take more than is warranted, which then means that they're going to be taking more of other products like acetaminophen as an example, which comes very commonly in OTCs, dextromethorphan, all which have risks if you exceed the recommended daily amount of those as well. So I could see that being a scenario where somebody would be taking more than maybe what's even labeled because, remember, these are over-the-counter products that anybody can

purchase and can take any amount that they prefer.

DR. COYLE: Thank you for clarifying that. That was a concern that I also share. I think not only overusing a single product, but if a patient were to not experience the effectiveness for that major symptom of nasal congestion, might they then consider switching to a different proprietary product that actually still contains phenylephrine? So I wonder not only about overusing those single products but, really, what combinations patients might end up with.

We haven't talked yet about the cost perspective, but I find that also to be concerning. I mean, these are costly products over the counter, so I'd be interested to hear more in a follow-up question on that aspect from our patient and consumer representatives. But for now, I want to continue in this vein, and I know that Dr. Amirshahi had her hand up as well, so I'd like to acknowledge her.

DR. AMIRSHAHI: Hello. Dr. Maryann Amirshahi. I wanted to make a comment as a medical

toxicologist. One of the things that we see with the phenylephrine, for the most part, is we don't get a lot of reports of significant toxicity or adverse outcomes; usually, it's more associated, once again, with the combination products that we see. I think we do have a moral obligation -- particularly when we talk about the amount of money that people were spending on these products, as was presented yesterday -- that we take that in totality.

Plus, in addition, if we have a medication that is ineffective, we may also have additional unrecognized costs in that patients, because it's not effective, may have more utilization of healthcare resources. For example, they may have unnecessary doctor or urgent care visits, or they may spend more on additional products, or be exposed to toxicity from the combination products.

I have to underscore that. Also, we do have an effective alternative in pseudoephedrine, and while there are some limitations there, the bar to obtain the product really isn't as high as was kind

of described; perhaps maybe in more underserved areas, but for the most part, I think that we have a safe and accessible alternative as well. That's really the only comments I had. Thank you.

DR. COYLE: Thank you. I appreciate that perspective, particularly from the the toxicology standpoint and what you may have seen in your clinical practice.

Dr. Ginsburg, please go ahead.

DR. GINSBURG: Thank you. Diane Ginsburg, University of Texas at Austin College of Pharmacy. I really appreciate the last two comments, specifically regarding the moral issue because I'm thinking about this from an ethical perspective in terms of trust that consumers have with their healthcare providers.

It is very frequent, as we have students who are completing rotations and recommending over-the-counter products, and I think about it from the ethical side of answering a patient's question in an OTC aisle, knowing the science behind that type of product, or a combination

product with phenylephrine, and knowing that the phenylephrine is not effective, and putting that individual, really, in kind of a dilemma situation, where if you're recommending something that you knowingly know is not effective, to me that just erodes trust that patients have with us. That's one piece of it.

The second piece, and I'm really glad -- I think it was Dr. Brittain who brought up the safety question related to the fact that these are combination products. I'm apologizing if I don't recall in the consumer study, if they talked about how many of the products were combination versus single-agent products. But regardless, the fact is that the majority of people take these products in a combination, so there's the propensity for patients to overuse and/or switch to other products with phenylephrine in them, and that to me, as a pharmacist, is very concerning. Thank you. Those are my comments.

DR. COYLE: Thank you, Dr. Ginsburg.

Dr. D'Agostino, I see your name is up.

Please go ahead.

DR. D'AGOSTINO: Yes. I think all of this is getting into all the things that I was thinking of when we were preparing for this meeting. The safety question I think has a lot of components, but there have been some great points raised about taking a drug that's ineffective, the risk of delay in care. One of the things that I think hasn't been raised is going a little bit deeper into that risk of delay in care.

There's the point of you may be delaying care for the common cold, but the one that we really haven't touched on is why most people are getting sick right now, which is we do have an ongoing pandemic where there are effective therapies that you could be taking, and we're also about to enter the flu season, so we have the opportunity to push people to more effective therapies.

So there's a real risk of spreading more disease, not pushing people to the drugs that actually work, not just pseudoephedrine but other

more effective drugs. Then the unnecessary cost is a big one, too, that I've definitely been thinking about, and not just having these drugs in combination products that shouldn't really be there, and maybe the over-the-counter therapies that are available would work fine without phenylephrine, and we could just remove them, and people could take their DayQuil for their cold, and they can be perfectly effective., or their Afrin for their allergies or whatever.

I think those are kind of the thoughts that are like what should people actually be taking for the common cold, allergies; if they just have their seasonal allergies that aren't super severe; where should people go if they do have COVID; how do they know if they have the flu; where should they actually be going, and what should they be taking, and how could they know, which I think we'll get into a little bit more this afternoon when we talk about how should we communicate to people. But that risk of delay in care and what happens if you take a drug that doesn't work are all the things

that I've really been thinking about here. I think I'll stop there.

DR. COYLE: Thank you. I appreciate you adding that perspective to our discussion.

Dr. Calis, we haven't heard from you before. Please go ahead.

DR. CALIS: Thank you very much; a lot of very insightful comments, and I appreciate the discussion. One of the things that just comes to mind -- and I don't want us to dismiss it -- is the issue that has been brought up about whether we're dealing with allergic rhinitis and how that's different from the common cold, et cetera, which if I step back and look at it from the traditional drug development paradigm, you typically see that we will do natural history studies.

We want to understand the pathophysiology. We want to identify potentially effective treatments, and do it in a systematic, organized way that helps us arrive at something that might be effective, based on our understanding of the disease progression, and based on the understanding

of the mechanism of action, and the various interventions.

However, in this particular case, with all the limitations that have been identified so far, I think we can go back and look at the entire body of evidence, and I think we've heard some pieces here. But I think if we step back and look at the three main areas -- the pharmacokinetics, clinical efficacy, and clinical safety -- if we look at the pharmacokinetics, as some of my colleagues have already identified very nicely, we have very low systemic exposure.

We know what this drug does. We know if we give it in a way systemically, we know what IV phenylephrine can do. We know that it could potentially have various cardiovascular effects, et cetera. So we already know what it can do physiologically. We haven't seen any major clinical safety signals probably because of the low systemic exposure. So the pharmacokinetics, the clinical safety data are corresponding, and now we have a larger body of evidence with more

contemporary studies looking at the clinical efficacy, and I think clearly -- clearly -- the data overwhelmingly support the fact that phenylephrine is essentially, in its current way that it's administered, ineffective and essentially acts like a placebo.

So I believe that the whole body of evidence, we've talked about the various aspects of the data that we have. I think they all basically confirm the fact that this drug is not effective and should not really be available because, again, all you're doing is you're extending something of, I think, the issues of ethics and so forth that have been brought up. I'm also concerned about the combination treatments, et cetera.

So those, I think, all support what has been said so far and what was quite eloquently said at the very beginning by Dr. Clement, who provided a nice synopsis of essentially what I feel as well. So I'll stop there. Thank you.

DR. COYLE: Great. Thank you, Dr. Calis. I think that was a nice bookend to some of our

earlier comments from Dr. Clement, just as you pointed out.

I know we still have some hands up, but I wanted to invite Dr. King to just comment from her area of expertise, if there's anything that stands out to you, Dr. King, regarding the studies themselves that you feel is worthy to bring back up before the AC.

DR. KING: Sure. Thank you. Tonya King, professor of biostatistics. No one was really asking questions about the meta-analyses. I was going to comment on that, but I really appreciated the discussion that was ensuing and didn't want to interrupt, and I really appreciated the comments that have been brought up this morning, even new things to think about.

I was going to make a comment about the meta-analyses just in terms of when reviewing a meta-analysis, it's important to look at a funnel plot of the sample size by the p-values. If there's a significant effect, you would expect to see larger studies with some small p-values and

smaller studies with potentially a range of small-to-large p-values. And if you visualize a funnel plot from the prior studies that were included in the meta-analyses, it's really the reverse that's happening. The smaller studies were the ones with the highly significant p-values, and due to that and the other issues brought up by the FDA statistician, I believe those studies are suspect. That was just a thought in terms of the meta-analyses.

I did go back and review to see what was different between the two meta-analyses that were performed, and actually, the CHPA group reanalyzed the same studies that the Hatton group analyzed, and when using the same studies and the same outcome, they did reach the same conclusion. But where they differed in what they presented was that they chose a different outcome, which is valid, but all that shouldn't -- with the prior, especially the Elizabeth lab studies, I believe it's suspect. I appreciate the more recent studies, the large, properly designed, powered, multicenter, well

controlled with current design and statistical standards, and I think that those results are pretty convincing. Thank you.

DR. COYLE: Thank you. We appreciate you weighing in.

I do think I have two committee members, two AC members, who have not spoken. So I just want to offer Dr. Blalock or Dr. Pisarik an opportunity to comment on the question at hand, the efficacy and pharmacokinetic data, or any of the previous topics that we've touched on. I'll pause for just a moment.

DR. BLALOCK: This is Sue Blalock.

DR. COYLE: Okay. Go ahead.

DR. BLALOCK: Okay. I've been quiet because I just think the evidence is pretty compelling, and I certainly concur with the gist that everyone has expressed. I think it's particularly compelling when you think about using more medication than recommended when you're not getting the effect after the first dose, and that raising safety concerns. So I just underscore what others have

said.

DR. COYLE: Thank you. Thank you for adding the weight of your input.

Dr. Pisarik, please go ahead.

DR. PISARIK: I mirror what everybody else has been saying. I don't think that the evidence supports a pharmacological effect from pseudoephedrine [sic]. Even if that 1 percent absorbed was significant, the studies don't show that it does anything in terms of nasal congestion. So I think the evidence is pretty clear that the pseudoephedrine really doesn't do much in terms of nasal congestion.

When I see patients with nasal congestion -- and I've worked in urgent cares before -- sometimes people come in, and it's hard to tell if they've got allergies or whether it's a cold, especially when people come in saying I've got this sinus infection that comes every September and April. Well, if it's twice a year, and they come in with nasal congestion, it's probably more allergies than anything else. But I usually tell

them for their congestion to use oxymetazoline nasal spray, followed 30 minutes later by a nasal steroid. And I tell them to do it twice a day for 3 days, and after that just go to once-a-day nasal steroid, and stop the oxymetazoline. I think a lot of times it does help with their symptoms and helps with their congestion, and they should feel better after that.

So again, I never prescribe pseudoephedrine. If anything, I say pseudoephedrine is what you need, and that's only behind the counter with a pharmacist.

DR. COYLE: Thank you. We appreciate your frontline experience with those situations.

Dr. Le, I know your hand was up. I was not ignoring that. We do have a couple of minutes if you'd like to make a final comment before we break.

DR. LE: No. I'll go ahead and discuss that -- I think we have another discussion topic, that I'll include that, my thoughts. Thank you.

DR. COYLE: Yes. You're welcome.

I don't see further additional comments.

Does anyone have anything that they would like to share from the advisory committee panelists that is new or has not yet been touched on, that you think is relevant for our scientific efficacy and pharmacokinetic data discussion point?

(No response.)

DR. COYLE: I would like to thank you all for a really thorough conversation and for all of your expertise in contributing to that discussion. Personally, I found it incredibly helpful, and I hope that you all did as well.

We will now take a 15-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topic during the break, and we will resume at 10:43 Eastern Time. Thank you.

(Whereupon, at 10:27 a.m., a recess was taken, and meeting resumed at 10:43 a.m.)

DR. COYLE: Hello, everyone. Welcome back. We've had a very good discussion in the first part of our meeting on the first discussion question, and we will now move on to our next question, which

is a voting question. Dr. Jessica Seo will provide the instructions for voting.

DR. SEO: Thank you, Dr. Coyle. This is Jessica Seo, DFO. Question 2 is a voting question, and voting members will use the Zoom platform to submit their vote for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote.

After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin. A voting window will appear where you can submit your vote. There will be no discussion during the voting question. You should select the radio button that is a round circular button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote.

Once all voting members have selected their vote, I will announce that the vote is closed. Please note there will be a momentary pause as we

tally the vote results and return non-voting members to the meeting room. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the list and each voting member will state their name and their vote into the record. You should also address any subparts of the voting question, which includes the rationale for your vote.

Are there any questions about the voting process before we begin?

(No response.)

DR. SEO: Alright. I don't see any hands raised. So since there are no questions, I will hand it back to Dr. Coyle, and we can begin.

(No response.)

DR. SEO: Dr. Coyle, you look like you're muted.

DR. COYLE: Thank you. Thank you for the reminder.

Okay. I will begin by reading question 2, the voting question, to the committee, and then we

will pause to see if there are any questions or concerns about the wording of the question itself. Question 2 for our vote, do the current scientific data that were presented support that the monographed dosage of orally administered phenylephrine is effective as a nasal decongestant? If yes, discuss what data you consider supportive. If no, discuss what additional data, if any, are needed to assess phenylephrine pharmacokinetics for efficacy.

Are there any questions about the wording, or any clarifying questions about the wording of this?

(No response.)

DR. COYLE: Seeing none, with no questions or comments concerning the wording of the question, we will begin the voting of question 2.

DR. SEO: We will now move non-voting participants to the breakout room.

(Voting.)

DR. SEO: Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

DR. SEO: There were zero yeses, 16 noes, and zero abstentions.

Dr. Coyle?

DR. COYLE: Thank you.

We will now go down the list and have everyone who voted state their name and their vote into the record. You may also include the rationale for your vote, and we'll start with Dr. Amirshahi.

DR. AMIRSHAHI: Maryann Amirshahi. I voted no. I think that the preponderance of evidence presented was really compelling, and that's really why. Thank you.

DR. COYLE: [Inaudible]

DR. KING: Hi. Tonya King from Penn State College of Medicine. I also voted no. I thought it was interesting. I think there was some new information this morning that the last panel actually voted similarly to a similar question, and then subsequently there was a question about whether there might be efficacy and what would be

needed further. So along with everyone else, I agree with the evidence shown today, and I just thought that that was interesting.

DR. COYLE: Thank you.

Dr. Le?

DR. LE: Jennifer Le from UC San Diego. I voted no based on the recent pharmacologic studies, the more robust clinical trials that included three multicenter, double-blind, randomized-controlled trials, as well as comments from the open hearing yesterday. I vote no in that I believe that oral phenylephrine 10 milligram is not efficacious for the symptomatic treatment of nasal congestion associated with both the common cold and allergic rhinitis.

For additional data, I would advise considering evaluating higher doses of oral phenylephrine in patients with common cold and allergic rhinitis, if possible, and evaluate drug penetration to the nasal mucosa, even considering the use of in vivo animal models, if needed. In addition, I recommend that the FDA firmly makes a

strong statement to the public and the drug sponsors not to use or consider any data or previous clinical trials that did not align with data integrity standards and confirmed by forensic analysis.

Lastly, from the consumer perspective, I recommend that FDA reconsiders the labeling of oral phenylephrine as GRAS-E, as it currently stands now, since this may lead to consumer confusion to the efficacy of the drug and the advisory committee's concern for patient safety that extends beyond just individual drug safety, encompassing both combination products and the potential for delayed and ineffective treatment. Thank you.

DR. COYLE: Thank you.

Dr. Blalock?

DR. BLALOCK: Yes. This is Sue Blalock, and I voted no. I think the evidence are pretty compelling that this medication is not effective, and really can't be effective because of the pharmacokinetics, and I don't really think that additional data are needed to support that

conclusion.

DR. COYLE: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: I voted no. Jennifer Schwartzott. At this point, I think enough studies have been done. I don't believe that additional trials would produce a different outcome. I feel that this drug in this oral dose should have been removed from the market a long time ago. The patient community requires and deserves medications that treat their symptoms safely and effectively, and I don't believe that this medication does that.

DR. COYLE: Thank you.

Dr. Clement?

DR. CLEMENT: Yes. Thanks. I voted no for all the reasons stated above. In addition, I agree and concur with the discussion that was held earlier about more efficacy really is a safety issue for delayed treatment. This isn't just, well, it's not doing anything badly; why not just continue it? It is a safety issue because the patients are being given the wrong thing, and it's

preventing them from getting the right thing.

DR. COYLE: Thank you. And will you confirm your name for the record?

DR. CLEMENT: Yes. Stephen Clement, Inova hospital system.

DR. COYLE: Thank you.

DR. CLEMENT: Thank you.

Dr. Calis?

DR. CALIS: Hi. Karim Calis from the NIH, and I voted no. I believe that the body of evidence from the pharmacokinetic studies, from the clinical safety data that we have, and from the more recent contemporary clinical efficacy trials all consistently corroborate the assertion that in this route of administration and at the monograph dosage, phenylephrine lacks efficacy. Thank you.

DR. COYLE: Thank you.

Dr. Figg?

DR. FIGG: William Figg from the National Cancer Institute. I voted no. I thought Dr. Meltzer's two randomized studies were compelling for lack of efficacy. I think those

were the best controlled studies that had been done with this particular drug. Also, the financial toxicity associated with an ineffective drug was overwhelming. It's amazing the amount of dollars being spent on something that has really no efficacy, as well as the poor bioavailability that, I agree, probably precludes any further studies of increasing the dose with such a low bioavailability and a high first-pass metabolism. Thank you.

DR. COYLE: Thank you.

Dr. Brittain?

DR. BRITTAIN: Kristy Brittain, Medical University of South Carolina. I voted no, based on the pharmacokinetic data and clinical data that was shared. I believe this is a long overdue change, and agree with the risk that would be associated with continued availability and use in the U.S.

DR. COYLE: Thank you.

Dr. D'Agostino?

DR. D'AGOSTINO: Emma D'Agostino. I voted no. I think that the newer studies were adequate and well designed, and showed that there is no

efficacy. Also, as we discussed, they showed a lack of efficacy in seasonal allergic rhinitis, and we do have the J&J study showing, reasonably, a lack of efficacy in the common cold as well. So we have pretty nice data showing the lack of efficacy broadly across all the indications.

I also thought that the PK data were convincing, showing that there is no bioavailability, which explains pretty nicely why we're not seeing efficacy, and I don't think that we need to show any additional data. I that what we have is pretty adequate to show that there is not any efficacy. Thank you.

DR. COYLE: Thank you.

Dr. Ginsburg?

DR. GINSBURG: Diane Ginsburg, University of Texas at Austin College of Pharmacy. I also voted no; similar comments. I do not believe that the evidence that was presented supports in any way the efficacy of this product remaining on the market. I don't believe that, at this point, doing additional studies in any way would provide us any

beneficial information that might change that opinion.

Similar to what others have said, I think the studies that were presented yesterday by Dr. Meltzer were very, very compelling, and I think really just kind of sealed it for me in terms of the lack of efficacy for a product. We really should not have products on the market that are not effective. Thank you.

DR. COYLE: Thank you.

Dr. Dykewicz?

DR. DYKEWICZ: This is Mark Dykewicz at Saint Louis University School of Medicine. I voted no. We now have compelling, convincing evidence that oral phenylephrine is ineffective at relieving symptoms of nasal congestion. The evidence is derived from multiple well-designed and performed clinical trials involving large numbers of patients. These include studies in allergic rhinitis by Horak 2009, Day 2009, Meltzer 2015, Meltzer 2016, and in the common cold, the Johnson & Johnson sponsored trial during the

2017-2018 cold season. I don't see any need to further assess oral phenylephrine pharmacokinetics or efficacy. Thanks.

DR. COYLE: Thank you.

Dr. Jones?

DR. JONES: Dr. Bridgette Jones. I voted no for all the reasons that were previously stated. We were shown the data that shows the very low bioavailability for phenylephrine when taken orally, leading to lack of drug at the necessary site for effectiveness. We also saw studies that showed in both the NAR studies and the clinical scoring outcome studies that there was no demonstration of efficacy for phenylephrine when taken orally.

So I think, overall, the data are pretty clear. I don't think additional studies would be necessary given that that we have well-designed rigorous trials both in patients with allergic rhinitis and studies conducted for the common cold.

DR. COYLE: Thank you.

Dr. Kim?

DR. KIM: This is Esther Kim, Fort Belvoir. I voted no as well. I think at the end of the day, we have basically no evidence that demonstrates any meaningful and lasting symptom relief, regardless of the cause of the actual congestion, whether it be for allergic rhinitis versus the acute upper respiratory formation of cold. I think at the end of the day, we are delaying meaningful treatment when there are available options, both over the counter and prescription; so therefore, we are essentially confusing our patients and consumers alike in being able to choose better options that would help them. I don't think any more studies are needed to demonstrate the same conclusion.

DR. COYLE: Thank you.

Dr. Pisarik?

DR. PISARIK: Paul Pisarik, Archwell Health. I voted no for all the reasons mentioned above. The studies don't show efficacy. As far as potentially doing other studies, I think we're kind of beating a dead horse. If we do 60 or 80 milligrams of phenylephrine, then we have to

start worrying about blood pressure increases since at 100 milligrams, blood pressure goes up by 10 points. I think there's a safety issue there, so I agree this is a done deal as far as I'm concerned. It doesn't work.

DR. COYLE: Thank you.

Maria Coyle, Ohio State University. I also voted no for all the reasons stated. I think we clearly have better options in the over-the-counter space to help our patients, and the studies do not support that this is an effective drug, and delaying care or other negatives associated with care far outweigh any potential, even in the future if this drug were studied at different doses. So I would not be in favor of additional studies at this time, along with my fellow panelists who stated the same.

So thank you all for your attention to this voting question. Just to summarize, we have a unanimous vote in regards to the question, so we do not believe as a panel that the current scientific data support the dosage of 10 milligrams of orally

administered phenylephrine as effective as a nasal decongestant, and by majority vote would not be in favor of additional studies exploring phenylephrine pharmacokinetics or efficacy of additional doses, although there was some disagreement on that point. Thank you all.

Since we have time before our lunch break, we will go ahead and move on to question 3. This is a discussion question again, so as has been our practice, I will just read the question to ensure that there is no confusion or wording clarifications that are needed, and then I will open the floor to our advisory committee members for broad discussion.

Question number 3, discuss whether the current scientific data that were presented support that a dose of orally administered phenylephrine higher than the monographed dosage would be safe and effective.

Are there any questions or comments concerning the wording of the question?

(No response.)

DR. COYLE: Hearing none, I will open up for discussion the question itself; any current scientific data that were presented that support a dose of orally administered phenylephrine higher than the monographed dosage as safe and effective?

We'll begin with Dr. Brittain.

DR. BRITTAIN: Kristy Brittain, Medical University of South Carolina. I would say prior to yesterday, I kind of thought that maybe higher doses would be reasonable for study, but we'll go back to the pharmacokinetic data that was shared, and really, to me, goes against considering additional studies of higher doses.

DR. COYLE: Thank you.

Dr. Calis, please go ahead.

DR. CALIS: Thank you. Karim Calis from the NIH. I believe that this would not be the course to go with. That's why I did not suggest any additional studies. We already know how this drug works. We already know its mechanism of action. We already know what this class of drugs does. We just know that in its current form, in the dosage

form that is currently provided at the current dosage, you have very low systemic exposure. So if we push the dose, it's possible that you might get additional systemic exposure, but with that, we already know that we will probably very likely encounter additional cardiovascular effects just as we would do from the entire class of those drugs.

So I think that would be the the wrong thing, and I don't think the data would support that. Could there be some efficacy at much higher dosage? Possibly, but with the corresponding increase in potential cardiovascular effects and safety issues. Thank you.

DR. COYLE: Thank you.

Dr. Clement, you may go ahead.

DR. CLEMENT: Yes. Thanks. Can you hear me?

DR. COYLE: Yes.

DR. CLEMENT: Steve Clement, Inova. Yes, I agree with my other colleagues. The systemic dose, or basically spillover effect, in terms of increasing blood pressure I think is a concern, and

we have other drugs. I mean, this has been a great seminar on learning how to treat stuffy nose, so there are lots of other things out there that are less risky and less chance of causing blood pressure problems.

DR. COYLE: Thank you, Dr. Clement.

I would raise my hand, Maria Coyle at the Ohio State University, just to add my perspective. I'm an ambulatory care pharmacist. I work in the clinic settings with patients around cardiac risk reduction. I can share that currently with my patients, I don't really have a lot of counseling points around the use of oral decongestants, although we certainly do talk about over-the-counter drugs and what would be appropriate for them and what might not be appropriate given their comorbidities.

I do think that at a higher dosage, I would want to know much more about any over-the-counter products that contain phenylephrine because of concerns about cardiac safety, and I also think that we might have a very different conversation in

an advisory committee about that balance between efficacy and safety at higher doses. So I think should we have those conversations, I would be curious to see that data, but as has been stated, we have alternatives currently that can be effective. Although the oral dosage form may be preferred by patients initially, I do think that effectiveness and maybe some patient education around which products are most effective might sway that decision in a well-educated consumer.

So just my thoughts here, and I'll recognize Dr. Le as well.

DR. LE: Jennifer Le from UC San Diego. I guess I was the one, or at least one, who recommended consideration to value at higher doses. I'm pediatric and infectious disease on the hospital side, so I don't see most amcare patients. I was coming from the perspective of not necessarily looking at higher doses for OTC indication, but it would be more for an inpatient, maybe a potential alternative perspective, because I do think the data is there that a higher dose may

be effective but, yes, that has to weigh into the consideration for increased blood pressure that we would see with this. So I'm coming from not the OTC perspective but as a prescribed drug, potentially, at higher doses.

DR. COYLE: Thank you, Dr. Le.

Dr. Kim?

DR. KIM: Just a couple of thoughts about whether or not a higher dose would then be useful of our resources that are already limited, considering we're at 2023 and discussing data post-2007 to look at the effectiveness of this, when we have decongestants that are available and much more effective topically, I'm not sure this is a good diversion of any of our efforts, whether it's higher dosing or just, in general, looking at phenylephrine again.

DR. COYLE: Thank you.

Ms. Schwartzott, please go ahead.

MS. SCHWARTZOTT: Jennifer Schwartzott, patient representative. The evidence showed, and the study showed, that you would have to go at

least over 40 milligrams, and then you start having the safety risk, and that's still even questionable with the efficacy. I think we have an ethical and a moral obligation to the patients. There are other alternatives out there, and hopefully other companies will come up with new medications in the future to replace this. But now that we know what we know, I think it's up to us to say this is where this ends.

DR. COYLE: I'm just scrolling to see if I have any other comments from the panel.

Dr. King, please go ahead.

DR. KING: Thank you. Tonya King. I was just going to comment that I thought it was interesting that in the FDA briefing document, this study wasn't discussed or reviewed, but there was a reference to an article in 1933 that performed an analysis on phenylephrine, and they stated that in their analysis, they calculated the minimal pressor dose, so the PD effect on blood pressure of oral phenylephrine was 70 milligrams, and they found the minimally effective dose to be approximately

120 milligrams.

So it seemed as though an effective dose would not be safe just based on that and in review of other prior studies. I thought that was interesting, and I agree with the other comments stated thus far, that it is not worthwhile to pursue higher doses of phenylephrine. Thank you.

DR. COYLE: Thank you.

Dr. Amirshahi?

DR. AMIRSHAHI: Maryann Amirshahi. I also agree that I don't think that we need to pursue this further. The preliminary data that we have looking at higher doses doesn't really suggest a benefit, and I think we really need to consider resource utilization. Robust, large-scale clinical trials are very costly, and I feel that we're going to reach a point of futility at some point. Then also, once again, in the interim, while we're kind of further evaluating this, what is the status, and how much will people spend on the products if it continues to stay on the market while we're investigating something further?

So I really feel that the cost benefit for these particular studies really isn't there when we look at it objectively, and we have readily available and several alternatives. We have pseudoephedrine, and we also have topical products, so it's not like there is a huge void that will leave patients without any alternatives. Thank you.

DR. COYLE: Thank you.

So I'm hearing a broad consensus that the advisory committee members do not necessarily support a higher dosage be explored for OTC use. I want to invite any alternative viewpoints, if there are such, amongst the committee members, or any additional information that hasn't been brought out as an argument for or against this approach that we have not yet covered. I want to be a good shepherd of your time, but I also want to make sure that all viewpoints are being heard.

(No response.)

DR. COYLE: So maybe a last call for any questions or comments related to this discussion

question.

(No response.)

DR. COYLE: FDA, I think our opinion has been shared loudly and clearly through this brief but very much aligned set of viewpoints.

Alright. We will move on to question 4, and again, we will follow our format, clarifying any comments or questions related to the wording of the question itself, and then opening up for discussion. I think this is the question where we should broadly explore the question.

So first things first, discuss the implications for and communication strategies to consumers of the current oral phenylephrine data. Let me know if there are any questions or comments around the wording, please.

(No response.)

DR. COYLE: Okay. Seeing none, I will open this question up for discussion, and I will begin with Dr. Clement.

DR. CLEMENT: Steve Clement, Inova Hospital, a student of allergy and sinusitis now, after this

amazing discussion. This is an amazing paper. This is Dr. Dykewicz's epic panel of rhinitis 2020. I applaud you for putting this together. I know how hard putting together a group of authors that's this long is. And in there, I went through it and read figures 2, 3, 4, and 5. It's basically a bible on how to treat this condition.

I also applaud the FDA for bringing him in. This is a loaded panel that knows how to treat this disease, so I would submit that Dr. Dykewicz should be head of that panel to basically consult to the FDA to come up with a wording of alternatives, and we have wonderful alternatives that we did not have in 2007 and all these other years. So that may have been the reason there was some ambivalence with the previous committees. There are tons of stuff out there that's available, that's safe, and effective, and over the counter.

DR. COYLE: Thank you.

Dr. Ginsburg?

DR. GINSBURG: Diane Ginsburg, University of Texas at Austin College of Pharmacy. This is

probably going to seem like a no-brainer, but two things are related to this. I think there's a huge potential for consumer concern that something that had been on the market for years, that there's a recommendation now to remove it, and seeing significant confusion with that. There were two public comments that were submitted by I'm presuming two patients who have used phenylephrine about please do not remove this from the market; this works for me; I don't have alternatives.

So I think it's going to be critical that they're in the communication, and there are assurances to patients who might still have these products, that no harm hopefully will come to them. That reassurance I think is going to be absolutely critical, and I think that's really important in terms of looking at any questions or criticisms related to the credibility of the FDA. I'm not being critical of the credibility, but I think that potentially that perception could be there.

The real positive here to me is I think this is a great opportunity from an educational

perspective to educate consumers on the fact that there are a lot more ways to treat these conditions, and I concur with what Dr. Clement just said about the bible of how to treat this. I think we have a real opportunity to do that, and I would encourage utilization of professional organizations, and medicine, and pharmacy to help assist with getting this message out and help in supporting the information that would come out from the FDA. I realize that there is a financial concern on industry, but I believe we were not asked to look at that, and if I have to balance finance versus patient safety, I will take patient safety any day of the week. Thanks for the opportunity to comment.

DR. COYLE: Thank you, Dr. Ginsberg.

Dr. Dykewicz, please go ahead.

DR. DYKEWICZ: Well, thank you for the last comments [indiscernible] from Dr. Clements. Rhinitis 2020 -- just a little bit of background -- was a major consensus document that was put together under the sponsorship of the major

allergy organizations in the U.S., the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology. We wrote the document with the thought that it did have a dual audience of not only healthcare providers but patients, because it does give guidelines looking at different severities and frequencies of rhinitis, both allergic and non-allergic, about what can be done.

So obviously, from my own perspective, I think that it could be very useful as a basis for patient education. I would note as an aside, this came out in 2020 as we were entering into the early phase of the pandemic, so I think it did not get the recognition or the publicity because we were busy with COVID. But the strategies for patient self-management even are there, and I think it's a matter of educating people that there are alternative approaches, and they're not being left out in the cold, and acquainting them with what the alternative approaches would be. Thank you.

DR. COYLE: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: Jennifer Schwartzott, patient representative. I think the consumers have a right to know that this medication that they've been taking for all these years shows a lack of efficacy. I think they need to understand the science behind it and why the further study was requested, and have an explanation in layman's terms of the reason behind the question and why we are making these recommendations.

I think it's really important that the FDA is very clear and very transparent. We need to build some trust, especially with this one, but with other medications and devices. I think that this information should be shared with doctors that are out there treating these patients, and also with pharmacists and other medical personnel so that they can explain to their patients why and what the problem is here. Again, transparency is key, and trust needs to be fostered with the public. Thank you.

DR. COYLE: Thank you for your comments.

Dr. D'Agostino?

DR. D'AGOSTINO: Yes. Emma D'Agostino. I have a lot of buckets of thoughts, but I'll start with going off with what Dr. Ginsburg said. I think there is definitely a lot of potential for confusion, so one bucket of thoughts that I have is around -- as a couple of people have said now -- definitely needing to find a way to really simply communicate what has happened, what is the FDA process for thinking about why are we pulling medication off the market. How do we go about this process? Why did we pull this specific medication? What was the data? What studies did we do? There may be questions about why did it take so long like we heard here over the past two days, and then where do we go from here?

As we said, people are not left out in the cold, but where are they going to go from here? What do I do if I have a cold? What do I do if I have allergies? What are my alternatives? There's going to be a lot to think about how we reach people. Is that at the stores, over social media,

at their pharmacies, at their doctor, on the radio, TV news? Literally, just where do you reach people, and then how do you communicate to people, and at least three buckets of communication of what did the FDA do, what is the data showing, why did they do it, and now where do we go from here? I think that's a lot of complex communication to think through.

The last thing I'll say for now is there are a couple of buckets of confusion that I can think of, which I also saw with those public comments. There's some confusion about what is even getting pulled from the market. Are people going to think that pseudoephedrine is getting pulled from the market? Are they going to think that intranasal phenylephrine is getting pulled from the market? Are they going to trust the combination products that previously had phenylephrine? The common products that aren't working, is it Afrin? Is it pseudoephedrine? So there's a ton of potential for consumer confusion that I think is going to need to be very carefully thought through with the

communication strategies. Thank you.

DR. COYLE: Thank you, and thank you for identifying not only the issue around phenylephrine's status changing, but particularly the complexity of the OTC space in which it resides, being part of combination products perhaps more often than as a single entity.

Dr. Brittain?

DR. BRITTAIN: Kristy Brittain, Medical University of South Carolina. I kind of have very similar comments to what were shared. One, I do think, as this was raised yesterday, there may be some question about the timeliness of some of the the studies' new data to now and why it took so long in order to get to this point.

Then second, I think it really more refers to those combination products. I would argue that there's probably a lot of patients that don't even know that they have taken phenylephrine because of the vast array of OTC products that include it. So I think seeing information about a drug no longer being available or pulled off the market, I think

is concerning, but I do think that the public may be concerned about that just because of its presence in so many different places. The OTC aisles are very, very full, particularly for cough-and-cold products, and phenylephrine is in many, many of them, so just, I think, emphasis on that is extremely important.

DR. COYLE: Thank you.

Dr. Amirshahi?

DR. AMIRSHAHI: Hi. Maryann Amirshahi. I had a couple comments. I think as far as communications go, I think we need to be transparent regarding the delay and also why we're withdrawing the product from the market. I think it's definitely worth stating that medications that were approved many years ago don't have the same data that they do now, so I think it's a good thing that we also communicate that we are reassessing the products that are out there when a concern arises.

I think we also need to be mindful in our messaging that there really isn't a lot of safety

concerns. If a drug is removed from the market, a lot of times it's related to safety concerns, and I think that we really do need to communicate that it was more of an efficacy issue as opposed to a safety issue. Additionally, I think we need to provide guidance to patients as to what are the next steps, what are their alternatives, what products will be available to them, and finally, what to do with the products that they have on hand. I know that I keep a bunch of these in my house for when we have sniffles; in fact, I have a little cold now.

But that being said, the other thing I think we need to do is really communicate with our providers because, often, communication from the FDA really doesn't reach the average person in many circumstances, but really engaging providers with regard to the data so that they can address any questions, because they have a much more intimate relationship with patients, I think is critically important. I went through pharmacy school and medical school, and I have taken courses on

over-the-counter medication, and I had no idea, until prepping for this, how limited the data was with regard to the efficacy of phenylephrine. That's all the comments that I had with regard to communication. Thank you.

DR. COYLE: Thank you.

I just want to summarize what we've heard thus far. I think concern that any change in status for OTC phenylephrine be communicated clearly and that the public be reassured as to a lack of effectiveness or a lack of efficacy as the driver for this change rather than safety concerns, and I think recognizing that some patients may be very in tune to the ingredients of their OTC products and may be very concerned that this product is not going to potentially be available, and maybe on the flip side, patients who are less in tune with the individual ingredients may in fact not even be able to discern a difference.

I think also recognizing that we've been discussing maybe an assumption that phenylephrine would be withdrawn from the monograph, but I want

to acknowledge that that's not really what we have voted on per se, so the FDA will have to make that determination. But regardless, I do think information about this meeting and this deliberation of the advisory committee is out in the media and maybe reaching the level of awareness of many of our patients, so regardless of the outcome of these deliberations, perhaps some careful communication needs to happen, and that should probably happen at multiple levels, reaching providers, patients, consumer groups, and maybe in a variety of formats.

I think we probably have some time for additional comments, so Dr. Le, please go ahead.

DR. LE: Thank you for that summary. Just two additional things I wanted to add. I'm in agreement with Dr. Ginsburg saying how do we spread the words? Of course, curious patients will come and find out for themselves, but the point of contact is still over the counter. So I think reaching out to definitely medical, as well as pharmacy organizations, and particularly ones that

involve the independent pharmacies, the National Community Pharmacists, NCPA, and others that have direct contact with OTC products, I think it's going to be very important to spread the words and really tackle each patient one on one. That would be great.

What I also found useful, especially during COVID, was a YouTube video, actually, that CDC put out on COVID transmission to really talk about the data, because the scientific data presented here could be hard to understand from the efficacy and pharmacologic data. So to make it in reasonable lay language form and through social media platform can help spread the word as well.

Lastly, from the consumer perspective, I think one of the confusions that consumers might get is GRAS-E classification. I know I probably learned about this in pharmacy school, but I really didn't see that GRAS component until recently when I served on the National Science Foundation that used this terminology for food. So I would say that most consumers when they see GRAS, it's like,

"Okay. It's safe. I can take it because it's food." So I'm wondering if consumers can be better educated on that terminology that we're using as well, and of course adding on the E component for efficacy. Thank you.

DR. COYLE: Thank you, Dr. Le.

Dr. Jones, please go ahead.

DR. JONES: Dr. Bridgette Jones. The only other things I would add is I agree that this is an opportunity for education, specifically to provide more education about the common cold and allergic rhinitis, and the natural history and course of these I think is really important and what the appropriate and effective medications are for treatment of each of these conditions.

Several years ago, cough-and-cold medications were removed from the market for very young children, and when that happened, we had an opportunity to do a lot more teaching with families and with patients about the common cold itself and that it's a self-limiting condition in most cases, and what the current effective treatments are. So

I think this presents another opportunity in all age groups to teach about that.

I think the other thing that maybe hasn't been mentioned in regards to education is also making sure that patients and consumers are informed of how to access pseudoephedrine behind the counter because it has been some time since it's been moved to behind the counter, so I suspect there may be some people in the public who may not be aware of even how to to access.

The other thing that I would mention again and just reiterate is making sure that the FDA works with trusted partners to get these messages out. For example, the American Academy of Pediatrics is one that has a broad voice and has a publicly available web page, so not only getting that message out to the providers but also to the patients and the families as well I think is really important, and then also making sure that the message is reaching those that are in rural and underserved areas, and developing plans specifically for those patient groups is important.

DR. COYLE: Thank you, Dr. Jones. And just to clarify, you were mentioning some education on putting medications behind the counter or accessing medications that were behind the counter, and you were referencing helping consumers understand how to access pseudoephedrine.

DR. JONES: Pseudoephedrine, yes.

DR. COYLE: Okay. I just wanted to make sure we were all understanding you correctly.

Dr. Blalock, go ahead.

DR. BLALOCK: This is Sue Blalock. I'll try not to repeat anything that others have already said. One thing, though, that I want to add, is we live in a very small world, and if this panel was meeting 50 years ago, it might take 24 hours for this to hit the news. Sitting here at home, and I just Googled this, NBC News, the headline on my iPhone, "FDA panel says common over-the-counter decongestant doesn't work."

So I think when you talk about communication strategy, FDA really needs to think about it a little bit in phases, and the first phase is what's

the message today? And hopefully FDA has already been working on this and has some messages in the bank to make sure that there's minimal confusion going on, on Twitter and Facebook as we speak.

Then phase 2 is that I doubt very much that FDA is going to make a a decision on this within the next week, so what are the messages that take place between now and the time that the decision is made? Then more to what other folks have been speaking to after the decision is made or when the decision is imminent, what the strategy is.

The only other thing that I'll say -- and this is as a behavioral scientist -- is people really don't like change, and this is going to change how the cold-and-cough aisle looks in the pharmacy, so FDA really shouldn't underestimate the communication challenges that are going to be associated with this, but that does not suggest in any way that they should not stay the course. That's it.

DR. COYLE: Thank you, Dr. Blalock, and I particularly appreciate your specific suggestions

in regards to the phases, thinking about that communication in a very ordered and longitudinal manner.

Dr. Pisarik?

DR. PISARIK: Paul Pisarik, Archwell Health. I just wanted to comment about the complexity of all the over-the-counter combination products that are out there. On the FDA's list that we got, there are 29 different categories of combination products that are out there for colds. If phenylephrine is taken out, it will shrink it down quite a bit just to 13 categories of combination products.

Something that would help me talk to my patients and patients talk to me would be a kind of a labeling system, where each category has a certain letter to it so that patients can look at a chart. If they want an antihistamine decongestant product, they go to product C, and then C would be labeled on all different medications that are over-the-counter combination products, and they can see all the different ones that are C, so they know

exactly what to get in terms of something that might help relieve their symptoms.

When I go to the cough-and-cold section of a of a store and I'm looking at the products out there, I'm scratching my head, and it takes me 10 or 15 minutes just to look through everything and read through all the labels to see exactly what I want. I mentioned this to the chairman 11 years ago when I first started my first term with NDAC, and he told me it'd be easier to be elected to Congress than to get this labeling change done. But I think in terms of educating patients and having them educate us as to what they're taking, I think that'd be a great step forward. One of the categories would be if you want an oral over-the-counter decongestant, then you have to go behind the pharmacy for the pharmacist to dispense the pseudoephedrine. Anyway, that's my little spiel on labeling complexity.

DR. COYLE: Thank you, Dr. Pisarik. I think on a few occasions recently, NDAC and its partners have asked the FDA -- have raised the bar, and have

set new expectations for what we would like to see happen, and I think they're listening. I hope they're listening. Thank you for adding that comment.

I'm going to call on Dr. D'Agostino.

DR. D'AGOSTINO: Yes. Emma D'Agostino. Just a small point going back to safety, if consumers are going to shift their use to other over-the-counter drugs, when we're thinking about communication strategies, one advantage of phenylephrine is that it is pretty safe. There aren't really any adverse events that we're concerned about, but for other OTC drugs, there are potential safety concerns. We know that if you use intranasal phenylephrine for a long time, just as an example, there are potential adverse events.

So that's just one thing to think about for communication strategies, that we really need to communicate on the safety of the alternative medications and really work that into the communication of your alternatives, and this is how they really need to be used. Thank you.

DR. COYLE: Thank you.

Ms. Schwartzott, please go ahead.

MS. SCHWARTZOTT: I was thinking about this is going to be a difficult transition if they do choose to remove this product from the market, but the drug companies have made billions of dollars off of this medication for all these years. All drug companies are very, very good at their commercials -- I remember the video yesterday with one of the speakers with the cartoon heads exploding -- and they've been making these promises that this medication can fix their nasal congestion.

So the same things can happen now. They can start marketing the products that will be left on the market. This is a good chance to share the education and share what's out there with guidance from the FDA and the public. But what's the most important is that the people are getting the correct medications. I like the labeling suggestions. I also like that pseudoephedrine is behind with the pharmacist because they can explain

to people if that is the right medication for them. There are a lot of people out there with cardiovascular risks that should not be taking that.

So it's a great chance for education. It is definitely possible to get this information out to the public. I mean, it's very interesting that what we've said has already made it to social media in this short of time; so just my two cents. Thank you.

DR. COYLE: Thank you.

Dr. Brittain, what would you like to add?

DR. BRITTAIN: Kristy Brittain, Medical University of South Carolina. There have been a few comments about labeling of over-the-counter products, and I think while maybe there are some improvements that can be suggested, I think it's a prudent educational point that patients are instructed about the drug fact labeling that is on over-the-counter products that does include what the active ingredients are and what their mechanism or use is. That I think is an important thing, but

it does require you to flip the box around or actually look at the drug fact labeling. So that is something that is there. It's on all over-the-counter products with active ingredients, and, again, guiding individuals to that I think would also be helpful.

DR. COYLE: Thank you.

Dr. Clement?

DR. CLEMENT: Yes. Sorry. Just one other comment. This is a little bit on the higher 30,000-foot view that maybe even the FDA commissioner may need to get involved in, is that this may be one of the first where a drug is actually taken off, not for a safety reason but because a look-back on efficacy. One of the issues that startled me when I was going through the documents that were sent is this is a safety issue that may have never happened because it was really sort of a chance that Merck did this study, and it was really a chance that J&J did this study, and that the FDA had due diligence to put their foot down and say this is not right.

If those studies didn't happen, it never would have been caught. So from a safety standpoint, we do a lot of safety issues in the hospital. This is in the category called a good catch. If you look at Sentinel events, how do you prevent Sentinel events? This is a good catch, and from a communications standpoint, maybe the commissioner or someone higher up could talk about that. With this new legislation that came through with the CARES Act and so forth, the FDA has the opportunity to do a look-back on some of these things that got grandfathered in that maybe did not get the methodology on GCP and so forth, and can actually catch these things and help public health from that standpoint.

DR. COYLE: Thank you, Dr. Clement.

If I were to summarize, again, the most recent comments for the benefit of the group, I think looking at some specific strategies; thinking about communication to both reassure consumers as to the availability of effective products going forward; as well as the importance of removing

products that are potentially ineffective as being primary, that transparency that was mentioned throughout.

Are there other additional perspectives? While I issue this last call, I just want to thank our consumer and patient representatives for sharing their perspectives in particular, as well as acknowledging Dr. Blalock's statement that change is hard, and for some patients it may be very challenging if their product of choice is not available.

It looks like FDA may want an opportunity to respond to some of these most recent comments, so I'm going to allow that, and then, Dr. D'Agostino, I'll circle back to you here.

So FDA go ahead.

DR. MICHELE: Thank you, Dr. Coyle. I appreciate that we have other comments. I thought we were at the end. But I do want to thank the committee once again for all of your thoughtful consideration. I do want to assure you that, yes, we are listening. As you were speaking, I was

typing frantically all of the advice that you're giving us, which we will certainly take back and consider, along with the public comments, and along with the comments from industry. We do have a docket for this.

I'd also note that for consumers, we have a number of websites up on cough-cold products, on allergy products, that talk about a variety of different alternatives, particularly for pediatrics and treating children with colds and upper respiratory infections. So thank you everyone. We appreciate all of the input.

DR. COYLE: Thank you, Dr. Michele.

Dr. D'Agostino, would you like to add another comment, please?

DR. D'AGOSTINO: Sure. Just two final thoughts. This is Emma D'Agostino. One that came up yesterday, but it was also one of the first things I thought of, as we've talked about, if phenylephrine were to become unavailable, this would have a pretty big impact on the market. And I know that we're not talking about the impacts to

industry, but CHPA did talk about how this could potentially have supply chain shortages, and that was one of my first thoughts as well.

So I think just something for the FDA to think about would be to really think about the roll-out of this decision in a really thoughtful manner for the industry side of things as well, to make sure that any impacts to consumers would be minimized, so that if we're telling them that they do have these alternatives, that they're going to actually be available on shelf. Then along that same thread, potentially try to minimize those impacts.

I kind of brought this up this morning, but this seems like a good opportunity to remind people that as we're going into the flu season and we're in another COVID surge, colds often look like -- COVID often has the same symptoms as colds, and flu often can mimic a cold, so there are also other drugs like Paxlovid, and we have Tamiflu, [indiscernible], so there may be other effective drugs that you could take, and what would those

steps look like, too. Thank you.

DR. COYLE: Thank you.

I don't see additional comments from our panelists.

FDA, is there anything that you would like to say that was not just captured by Dr. Michele? Any final thoughts for us?

(No response.)

**Adjournment**

DR. COYLE: I would say to the FDA, thank you for engaging us in this conversation, and thank you to the panelists. As we close, I'd really like to applaud your efforts, the wide variety of perspectives that you offered, really highlighting the importance of our role in protecting the public trust and being advocates for the public, making sure that products that are available to them are not only safe but highly effective and worth their hard-earned investment for health.

I greatly appreciate those of you who participated throughout the conversation. I think everyone contributed from their level of expertise.

I want to thank the Consumer Healthcare Protection Agency also for their contributions and their willingness to answer questions as we went through these past few days, and the speakers in the open public hearing, particularly those that devoted quite a bit of time in making sure that their data was seen and viewed through the lens of a scientist and particularly helpful for all of us.

So at this point, given that our business is concluded, I will go ahead and adjourn the meeting. Thank you all, and enjoy the rest of your day.

(Whereupon, at 11:57 a.m., the meeting was adjourned.)