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FOOD AND DRUG ADMINISTRATION

JOINT MEETING OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE AND PEDIATRIC ADVISORY COMMITTEE ON

"SAFETY AND EFFICACY OF OVER-THE-COUNTER COUGH AND COLD PRODUCTS MARKETED FOR PEDIATRIC USE"

OCTOBER 18, 2007

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P R O C E E D I N G S

DR. TINETTI: Good morning. We're going to get started and want to welcome you all to these combined Pediatric and Nonprescription Drugs Advisory Committee. I'm going to read a short statement. Then I'll have the Committee introduce themselves.

For topics such as those being discussed at today's meeting, there are often a variety of opinions. Some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the government, in the Sunshine Act, we ask that the Advisory Committee members take care that their

conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However,

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FDA will refrain from discussing the details of this meeting with the media until its conclusion. A press conference will be held in the Distance Learning Room Number 9170 immediately following the meeting on Friday.

Also, the Committee is reminded to please refrain from discussing the meeting topic during the breaks or lunch. Thank you.

We will now have the Committee introduce themselves. I'm Mary Tinetti, Department of Internal Medicine at Yale, and I'm the chair of the Nonprescription Drug Committee and this is my co-chair.

DR. RAPPLEY: Good morning, I'm Marcia Rappley. I'm chair of the Pediatric Advisory Committee and I want to thank everyone for coming out to address this really important issue on behalf of the agency and also on behalf of children and pediatrics. And that includes members of the audience, too and your vested interest in this important issue. So thank you for the time and energy you're putting into this as well.

I'm from Michigan State University in the College of Human Medicine, and my area is developmental and behavioral pediatrics.

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DR. TINETTI: I'm going to have the Committee now introduce themselves. We'll start at this end and just remind you to put your "talk" button on to introduce yourself and then turn it off.

DR. GOLDSTEIN: I'm George Goldstein. I'm a board certified pediatrician who spent 17 years in practice and the next 32 in the pharmaceutical industry where I had the privilege of chairing the American Academy of Pediatrics Clinical Pharmacology section for two terms.

DR. GAROFALO: My name is Elizabeth Garofalo and I'm a pediatric neurologist by training, and I have been in the pharmaceutical industry as well and currently am an independent consultant.

DR. RICH GORMAN: I'm Rich Gorman, a pediatrician who represents the pediatric health care organizations at

this table.
DR. CALHOUN: Good morning. My name is Bill Calhoun. I'm a professor of medicine at the University of Texas Medical Branch in Galveston. My training is allergy immunology and pulmonary diseases.
DR. NEWMAN: I'm Tom Newman. I'm a general pediatrician and professor of epidemiology and

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biostatistics and pediatrics at UCSI.
MR. COHEN: And good morning everyone. My name is Mike Cohen. I'm a pharmacist and head of the Institute for Safe Medication Practices. Our focus is on medication safety, medication error prevention.
DR. ATKINSON: And my name is Prescott Atkinson and I'm an associate professor of pediatrics and allergy and immunology at the University of Alabama in Birmingham.
DR. JOAD: I'm Jesse Joad. I'm a professor of pediatrics at University of California-Davis and I'm board certified in allergy and pediatric pulmonology and have a Masters degree in clinical pharmacology.
DR. TAYLOR: I am Robert Taylor. I'm an internist by training, and a clinical pharmacologist. I'm from Howard University College of Medicine where I'm professor of medicine and pharmacology.
DR. GRIFFIN: I'm Marie Griffin and I'm a general internist and pharmacologic epidemiologist. I'm at Vanderbilt University. I'm professor of preventive medicine at Madison.
MS. HEWITT: I'm Jan Hewitt. I'm at the University of Michigan. I'm currently the Director of Institutional

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Review Board. I have a background as a registered nurse. I also hold a JD from the University of Michigan.
DR. SHRANK: I'm Will Shrank. I'm an internist. My academic position is in the Division of Pharmacal Epidemiology and Pharmacal Economics at Brigham and Women's Hospital at Harvard Medical School.
DR. D'AUGUSTINO: Ralph D'Augustino, biostatistician from Boston University.
DR. CLYBURN: I'm Ben Clyburn. I'm an associate professor of medicine, Department of Internal Medicine at Medic University, South Carolina, member of MBAC.
DR. PARKER: I'm Ruth Parker, Professor of Medicine,

Emory University School of Medicine, board certified in medicine and in pediatrics and work in health literacy.

MR. LYONS: Good morning. I'm Darrell Lyons, the designated federal official for the Nonprescription Drug Advisory Committee.

DR. BIER: I'm Dennis Bier. I'm a professor of pediatrics at Baylor College of Medicine, and I'm an endocrinologist who also has a specialty in nutrition.

DR. CNAAN: I'm Avital Cnaan. I'm professor of biostatistics and pediatrics in the University of

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Pennsylvania School of Medicine and Children's Hospital of Philadelphia.

DR. NEIL: I'm Richard Neil. I'm a residency program director and family medicine and community health at the University of Pennsylvania.

MS. CELENTO: I'm Amy Celento and I'm the patient representative to the Pediatric Advisory Committee.

DR. DAUM: I'm Robert Daum. I'm a professor of pediatrics, a specialty in infectious diseases at the University of Chicago.

DR. DURE: I'm Leon Dure. I'm a professor of pediatrics and neurology at the University of Alabama at Birmingham.

DR. ROSENTHAL: I'm Jeff Rosenthal. I'm a pediatric cardiologist at the Cleveland Clinic, and I have a Ph.D. in epidemiology and I serve on the Pediatric Advisory Committee.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I'm a pharmacal epidemiologist at the University of Pennsylvania.

DR. MCMAHON: Ann McMahon. I'm a pediatrician with a background in infectious disease, and I'm representing

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the Office of Surveillance in Epidemiology at the FDA.

DR. NELSON: Skip Nelson. I'm a pediatrician with training in critical care and immunology, and I'm representing the Office of Pediatric Therapeutic for the FDA.

DR. SCHIFFENBAUER: Joel Schiffenbauer in the Office of Nonprescription Drugs, FDA.

MR. GANLEY: I'm Charlie Ganley. I'm the Director of the Office of Nonprescription Products, FDA.

MR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs at FDA.

DR. TINETTI: Well, thank you and welcome to all of you. Darrell Lyons will read our Conflict of Interest Statement.

MR. LYONS: Thank you. Before I read the Conflict of Interest, I would like to remind everyone to please silence your cell phones, if you haven't already done so. And also, I would like to identify the FDA press contact, Susan Cruzan and Christopher Kelly. If you're in the building, if you could just okay. Thank you.

The Conflict of Interest Statement: The Food and Drug Administration is convening today's joint meeting of

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the Nonprescription Drugs Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exceptions of the industry representatives, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and consultants of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflict of interest when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers

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to special government employees and regular government employees with potential financial conflicts when necessary to afford the committees' essential expertise.

Related to the discussions of today's meetings, members and consultants of these committees who are special government employees have been screened for

potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and for the purpose of 18 U.S.C. 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, gratis, teaching, speaking and writing, patents and royalties and primary employment.

Today's agenda involves discussions of the safety and efficacy of over-the-counter cough and cold products marketed for pediatric use. This is a particular-matters meeting during which specific matters related to cough and cold products will be discussed.

Based on the agenda for today's meeting, and all financial interest reported by the committee members and consultants, conflict of interest waivers have been issued

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in accordance with 18 U.S.C. 208(b)(3) and 712 of the Food, Drug and Cosmetic Act to Dr. Ralph D'Augustino for his duties on a data safety monitoring board on an unrelated study for an affected firm. Dr. D'Augustino receives between $10,001 to $50,000 per year for his services.

The waiver allows Dr. D'Augustino to participate fully in today's deliberations. FDA's reason for issuing the waivers are described in the waiver document, which are posted on the FDA's website at www.FDA.gov/ohrms/dockets/default.htm. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Office, Room 630 of the Parklawn Building.

A copy of this statement will be available for review at the registration desk during this meeting and will be included as part of the official transcript.

Drs. George Goldstein and Elizabeth Garofalo are serving as the industry representatives acting on behalf of all regulated industry. Dr. Goldstein, a pharmaceutical consultant, is a retired employee of Sterling Drugs, Incorporated. Dr. Garofalo is employed by

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the Michigan Technology and Research Institute.

We would like to remind members and consultants that if the discussions involve any other products or firms not

already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement and the exclusions will be noted for the record. FDA encourages all participants to advise the committees of any financial relationships that they may have with any firms at issue. Thank you.

DR. TINETTI: Thank you, Darrell. We're going to move on now, first, to the FDA presentations. And for the Committee members, if you look, your packet does have a list of the questions that we're going to be addressing. So you might want to have a look at that to give you some background for our discussions over the next day and a half.

Our first presenter will be Joel Schiffenbauer, the deputy director who will discuss the OTC cough and cold products used in children.

DR. SCHIFFENBAUER: Good morning. I'd like to welcome everyone to the Joint Nonprescription Drugs and

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Pediatric Advisory Committee meeting to discuss the use of cold and cough products in children. I'd especially like to thank the committee members for their efforts and look forward to the discussion and recommendations.

My name is Joel Schiffenbauer. I'm the Deputy Division Director in the Division of Nonprescription Clinical Evaluation in the Office of Nonprescription Products, and I'd like to offer some introductory remarks.

I'd like to being by briefly reviewing the agenda for the next two days. Following my introduction, you'll hear a presentation regarding the development of the monograph, and specifically, the cold and cough monograph. Following that, you'll hear from several of the petitioners as well as several industry representatives.

In the afternoon, you'll hear from FDA representatives regarding safety and efficacy, medication errors, the use of pharmacokinetic data to determine dosing in children, an example with clinical studies in children for allergic rhinitis as an example of drug development in children.

So to begin, we're convened today to address the rather simple-appearing question, "Are cold and cough

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products safe and effective in children?" But this question will serve as the basis for the discussion over the next two days.

In March of 2007, the agency received a citizen petition regarding just this question. The petition makes the following points. Children are frequently afflicted by the common cold. A growing body of evidence demonstrates that these products are not effective in young children. And finally, although typically considered safe by parents and pediatricians, misuse has lead to the significant adverse affects in children under 6.

Based on these conclusions, the petitioners asked the agency to take three actions, which I've outlined in the next few slides.

(Slide)

DR. SCHIFFENBAUER: First, to provide a statement to the public explaining that OTC cough and cold products have not been shown to be safe and effective for the treatment of cough and cold in children under 6 years of age. Second, to notify manufacturers of these products whose labeling uses such terms as "infant or baby" or

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display images of children under the age of 6, that such marketing is not supported by scientific evidence and manufacturers will be subject to enforcement action at any time.

And third, to a amend the Code of Federal Regulations, Section 341, which is the cold and cough monograph, to require that labeling for OTC cold and cough products state "These products have not been found to be safe or effective in children under 6 and these products should not be used for the treatment of cold and cough in children under 6 years of age."

The petitioner is therefore requesting that the final monograph be amended, which will occur through a rulemaking process involving input from many sources. The recommendations of this committee may serve as the initial step in that process.

The ingredients under discussion can be found described in the cold and cough monograph published in the Code of Federal Regulation and were the result of a process whereby an outside panel of experts convened in a

public discussion similar to the one today to review the efficacy and safety of OTC products marketed prior to

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1975. At that time, there were over 300,000 OTC drug products available, including 800 active ingredients in multiple therapeutic categories.

As a result of the expert panel recommendations and additional public comment, the agency published in C.F.R. Section 341, the monograph entitled Cold, Cough, Allergy, Bronoc-Dialater and Anti-Asthmatic Drug Products for Over-the-Counter Human Use, and included the following therapeutic categories listed here.

In addition, the monograph provides the following information: permitted active ingredients, permitted combinations as well as specific labeling recommendations, including statement of identity, indications, directions for use, warnings, and a section entitled Professional Labeling, which are dosing directions provided to health care providers, but are not found on the drug facts label nor available to the consumer.

I've listed some of the examples of combination products permitted by the monograph. There are a number of others. These combinations were permitted to allow for the concomitant treatment of multiple symptoms with a single product. It should be also noted that at present

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all indications for each ingredient are allowed on the label. So for example, the combination of a decongestant and antihistamine, the label may contain both the cold indication and the allergic rhinitis indication.

At this point I'd like to take a moment to provide some information on the magnitude of use of these products. And for this, I turn to IMS Health national sales data. The data provides, in units, either tablets or for liquid formulations in milliliters, the amount of drug purchased by retail and non-retail settings, and may serve as a possible surrogate for use, assuming that facilities purchase drugs in quantities reflective of actual patient use.

(Slide)

DR. SCHIFFENBAUER: This slide show the total units sold for a combination OTC cough and cold products. Along the X-axis are the Years 2002 to 2006 and along the Y-axis

is the number of units sold in billions. The specific ingredients listed are shown on the right-hand side.

As you can see, in each year approximately 36 billion units were sold and the number remains fairly constant over the years. However, of note is between 2005

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and 2006 the drop in sales of pseudo-ephedrine and the increase in sales of phenylephrine is correlated with pseudo-ephedrine being placed behind the counter.

This figure provides data on total sales, but we're unable to determine how much use is by adults and how much by children. However, the next slide provides sales data for concentrated drop formulations, which is likely to be a surrogate for use by very young children.

(Slide)

DR. SCHIFFENBAUER: Again, this figure shows total units sold for combination cough and cold products of oral drop formulations. In any one year, there are approximately 190 million units sold. Again, you can note the drop in sales of pseudo-ephedrine and the increase in phenylephrine. These figures then provide a context for the extensive use of these products in young children.

Back to the original question "Are cold and cough products safe and effective in children?" In order to address this question, we need to examine the data supporting efficacy and safety of these ingredients, and this will be the focus of a number of presentations. You will hear later on a summary of available studies in

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children and some of the limitations of the studies performed to date.

You will also hear about the use of pharmacokinetic data to determine dosing in children, and we will present the pharmacokinetic data we have for two ingredients, chlorpheniramine and pseudo-ephedrine. The E11 guidance document entitled Clinical Investigations of Medicinal Products in Pediatric Population is found in your background package and describes the agency's thinking on the extrapolation of efficacy data from adults to children.

You will also hear about the development of drugs for the symptomatic treatment of allergic rhinitis in children as an example of how the pulmonary division

approaches drug development in children.

In regards to safety, you will hear about examples of medication errors that have been identified in our adverse event reporting system. You will also hear a summary of case reports and case series in the literature and a detailed analysis of adverse-event reports and test data, which is the National Poison Control database.

I'd like to take a moment to describe some of the

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data from the Maryland Poison Control Center as an example of safety concerns and why we need to examine all of the data very closely. In 2004, there were 1,100 calls to the Poison Control Center in regards to cough and cold medicines for children under five. This number appears striking, but needs to be put into some context.

Although there were 1,100 calls for cold and cough medicines, there were also 1,400 calls for topical products. Further, in terms of clinically important outcomes, there were five cases coded as having symptoms consistent with an outcome of moderate effect and all had complete resolution with supportive care. All five cases, except one, were acute, accidental overdose. That is, children inadvertently took medication.

Again, this data points out the need to look at it very closely and understand what it actually is telling us.

Before I close, I'd like to outline some of the points for the Committee to consider as they listen to the presentations, and for which you will be presented as questions later on.

First, we'd like you to consider if the disease

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process is similar in adults and children. We are not aware of data that shows that the disease process is different from children to adults in regards to, for example, the types of viruses, the immune response, or even the clinical presentation. However, you should consider whether anatomical differences such as airway size, for example, or other factors are sufficient to preclude the use of extrapolation of efficacy data from adults to children.

If you feel that the disease process is similar, is extrapolation of efficacy data appropriate? And if so,

what additional data is needed? And if not, are clinical studies needed? We'd also like to ask you what do the published studies contribute to our understanding of the efficacy. Do they, in fact, demonstrate that these products are not effective in children?

Next, are there safety issues that can be identified even when these drugs are used at the correct doses? What contribution does unintentional overdosing make to the overall safety profile of these drugs and what factors might contribute to unintentional dosing? And importantly, are these cases preventable?

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We'd also like to ask you are there ages for which these products should not be used? And if the products are labeled "do not use," should this apply to consumers as well as to health care providers, such that no one will be using these products. And finally, how should we address the use of combination products and the potential for medication errors when products contain multiple ingredients?

Lastly, I would just like to remind you that we are interested in your input. The agency has not reached any final decisions as to actions to be taken in response to the Citizens' Petition and any recommendations you hear today should not be considered final decisions.

Again, I would like to thank the Committee for their efforts and look forward to the discussion. And with that, I end and turn the meeting back to the Chairs. Thank you.

DR. TINETTI: Thank you, Dr. Schiffenbauer. If the Committee will hold the questions, if there are any questions, we'll be able to get to those in just a minute.

Our next presenter will be Marina Chang, who is the team leader in the Office of Nonprescription Products, and

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she's going to be discussing the regulatory history of pediatric cold and cough products.

DR. CHANG: Good morning. My name is Marina Chang, IDS team leader from the Office of Nonprescription Products.

This morning I will first talk about the OTC monograph drug process. Then I will go into the regulatory history of the cough/cold monographs with

special emphasis on pediatric dosing. Then I will tell you about a public comments proposed extended pediatric dosing schedule, which for all OTC drug products that FDA have published in the Federal Register.

Before I start my talk, I just want to show you a slide of pediatric cough/cold product in a local drugstore.

(Slide)

DR. CHANG: This is before the voluntary recall of the infant product last week. And here is the recalls. I just want to show you.

(Slide)

DR. CHANGE: This is has been recalled. This has been recalled and this has been recalled. So you can see

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there are still a lot of products that one can select from.

So do you know how these products are being regulated? I'm going to tell you now. All OTC products are regulated by one of two means. One is the new drug application or NDAs, or under the OTC drug monograph system. OTC NDAs are like prescription NDAs, are submitted by drug manufacturer for the specific products like Claritin, Advil cold and sinus; and the data provided in this is confidential.

And the drug manufacturer must receive approval from FDA for the specific products and its labeling prior to marketing, whereas monographs are active-ingredient specific. And here we would normally talk about chlorpheniramine, pseudophedrine, brompheniramine, and dextromethorphan. And the data reviewed in the monograph will be public information. And anyone can market a monograph product with the active ingredient and the labeling as stated in the monograph.

I would say most of the cough/cold products on the market today are being marketed under the monograph system. So what are these monographs and how did they

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come about? A review of the OTC drug was begun in 1972. And at that time, there were over 300,00 drug products; and a review of all these products, individually, simply wasn't feasible. So the agency decided to review in the individual active ingredients. Many of which were common

to more than one product. As a matter of fact, there were over 800 active ingredients at that time, and they were classified into different therapeutic categories.

Then the active ingredients in each category were initially reviewed by an advisory review panel. This panel consisted of scientific experts from outside the FDA. The panel will review, evaluate, and categorize the active ingredients into Category 1, which is generally recognized as safe and effective, and then Category 2, not safe and effective, or Category 3. That means they cannot determine whether the data submitted will determine it to be safe and effective and more data will be needed. And then they will prepare a report and present this report to the FDA.

After the panel's report, then the OTC rulemaking or what we sometimes call regulation-making process begins as a three-phase process. The first phase, the panel's

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report is published in this Advance Notice of Proposed Rulemaking. Sometimes we will call the ANPR, and a public comment period will follow, which will allow public and industry to submit comments.

In the second phase of the review, based on the comments received, a tentative final monograph will be published. What we sometimes call TFN, and again, this is followed by a public comment period.

In the third and last phase, based on the additional comments and information submitted, the agency developed a final rule, a final monograph. This final rule becomes the effective regulation for that particular ingredient or class of drug.

Now, what is in a drug monograph? A drug monograph lists the active ingredients, which are generally recognized as safe and effective. And for each ingredient, we will specify the dosage from the dose of concentration and then the permitted combinations.

A permitted combination means that a product may combine two or more generally recognized as safe and effective ingredients when each ingredient contributes to the claimed effects and none of the ingredients will

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decrease the safety and effectiveness of the other ingredients, and that combination is a rationale therapy.

As a matter of fact, the cough/cold monographs allow 28 various combinations, and Dr. Schiffenbauer had just shown you some examples in his talk.

In addition to the listing of active ingredients, a monograph will provide the required labeling. That is, the uses, the warnings, and directions. And no one is allowed to deviate from this labeling under the monograph process, except there is some flexibility in the uses section. Also, in some monographs there is a professional labeling section.

A professional labeling is where information can only be available to and advertised to health care professionals for conditions that cannot be self-diagnosed or safely treated; for example, aspirin to treat rheumatoid arthritis or antihistamine for children under 6 years of age, which is pertinent to our discussion today. And this information will not be available or allowed under OTC drug facts label.

Now, I have given you a quick view of the monograph process and what is in a drug monograph.

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Now, I will talk about the regulatory history of the cough/cold drug products, with special emphasis on the pediatric dosing. Much of what we have today for the cough/cold monograph drug products were based on the cough/cold panel's review study in 1972. The cough/cold panel applied the standards for safety and effectiveness as stated in this regulation, by reviewing the clinical studies and using the extensive marketing experience for the active ingredients in these four categories that we're going to talk about today.

(Slide.)

DR. CHANG: In this slide, I'm showing the total number of active ingredients the panel had reviewed for each category. You can see there's a total of 92 ingredients for these four categories. And on this column, you see that a total of 35 make it to the final rule. And you have a complete listing of the final monograph for each category in your background package. If you want find it, it's in volume 2, section 1 and tab 3.

Now, let's turn to the pediatric dosing considerations. The panel stated that, traditionally,

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dosing for infants and children has been based on weight, body surface area or age of the child as a proportion of the usual adult dose. However, the panel noted that data on use in children for most drugs is negligible or nonexistent, and dosing in particular individuals depends on manufacturers. Ideally, pediatric dose should derive from clinical trials with children, but recognize the extreme difficulty in conducting such clinical trials.

The panel also noted that the need to make recommendations for pediatric dosage is pending on data. The panel also recognized that determining children's dosage based on age would be the most convenient and easily understood because most parents or caregivers will know the child's age, but recognizing that this is the least reliable method because of the large variation in weight of patients in a specific age. Because OTC products has a relatively wide margin of safety from the adverse events reported and from the time and extent of use, the panel concluded that dosing recommendations should be based on age.

In order to provide the needed pediatric dosing, the panel also sought assistance from a panel of

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pediatricians. This panel was convened and met concurrently with the cough/cold panel in 1974. Based on the recommendations of the special panel, the cough/cold panel recommended the pediatric dosing schedule, as shown in here. That is children 6 to under 12 years of age one half the adult dose; and children 2 to 6 years of age, one quarter the adult dose.

The dosing directions for children under 2 started by saying, "advise and supervision of a physician" to "except under the supervision of a doctor" to what is currently stated in the drug facts labeling in plain language as "consult a physician or ask a doctor." And the Advanced Notice of Proposed Rule of ANPR with the panel's recommendation for this pediatric dosing was published in the Federal Register in 1976.

And through the rulemaking or regulation-making process, the ANPR-tested final rule was published was finalized 10 years later in 1987, and the expectorant 12 years later in 1989, and so on. And the last cough/cold

monograph, that is the cough/cold-permitted combination, was finalized 26 years later or five years ago in 2002.

Now, I will tell you about a public comment proposed

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standardized pediatric dosing schedule for monograph ingredients that FDA has published in the Federal Register.

During the course of the FDA's OTC drug review, the Advisory Review panel varied their pediatric age range dosing recommendations. For example, the cough/cold product, the panel recommended two dose divisions. It's 2 to under 6 and 6 to under 12, whereas, for the internal analgesic it's a five-dose age range. It's 2 to under 4 and then 4 to under 6, 6 to under 9, 9 to under 11 and then under 12. So no panel addresses the differences in pediatric age range and the impact that will have on the ability for manufacturing and labeling a product with this various dosing schedule when they are combined.

So FDA published a Notice of Intent in 1988 to revisit the pediatric dosing paradigm. This notice stated that FDA is considering proposing a rule concerning dosing information for children under 12 years of age for OTC products. FDA also published a suggested dosing scheme based on age and weight and fraction of adult dose. This was based on the public comments. In the next slide, I will show you this dosing scheme.

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(Slide)

DR. CHANG: And this is the dosing scheme that we published based on the public comment and based on age, weight and then the dosing unit for each age and weight group. On the right-hand column, again, you can see I'm showing the equivalence to the adult dose. And you can see this suggested dosing schedule is still a fraction of the adult dose.

After the publication of the notice, we received varied comments. We received comments opposing the suggested standardized pediatric dosing schedule because this comment stated that the current dosing approach as published in the rulemakings for the cough/cold, you remember, is the two division and for the internal analgesic, the five age division, provides extremely safe and effective dosing and no changes should be I'm sorry.

And they also solicited comments on how pediatric dosing information should be presented in the labeling. Should it be age and weight-based dosing or weight and age-based dosing or just age or weight? And also, should there be greater subdivision of age ranges? The cough/cold is to the internal analgesic was five, so is

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there any other dosing age ranges or are there other approaches? We were open for comments.

After the public occasion of that notice, we received varied comments and we received comments saying that no change should be made. And then, also we received one comment that pointed out that the age range with corresponding weight range do not agree with the 1979 National Center for Health Statistic Data.

We also received comments requiring pharmacokinetic data, and there was comments saying that in addition to the weight/age dosing, we should also include the length/height-based dosing and service area dosing.

(Slide)

DR. CHANG: Since there was an absence of actual pediatric dosing data and ANDENT meeting was convened in 1995. Here at this meeting we sought the committees' advice on pediatric dosing and labeling for OTC products. So we asked them to provide advice on pediatric dosing and labeling. Should it be age, weight, height or length, body service area or a combination of these four or just individual? And the committees' recommendation was weight, then age.

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And then we asked them is the current dosing approach that means the two doses for the cough/cold and the three dose for the internal analgesic an adequate dosing approach? And the committee said the two-dose division is not adequate, but the multi-dose division cannot be used for all OTC products.

The third discussion was should systemic pediatric dosing range for specific ingredients and different classes of OTC drug products be the same? And their advice was case-by-case basis.

And then we asked them should a calibrated dosing device be required because we would like to see if a calibrated dosing device is accompanying the product, then

we would give a more accurate dosing. Again, their answer was not required, but it's nice to have.

And our last question was asked is what is the minimum age/weight to appear in the labeling, and should this be different for certain classes of drugs? And the advice we got was depending on the drug.

Since the 1995 ANDENT meeting, due to varied comments received from the 1988 Notice of Intent and no data, especially pK data has been submitted to support the

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revisions of pediatric dosing, so the current pediatric dosing for the cough/cold drug products, the monograph drug products are still based on the cough/cold panel's original recommendation. That is, remember my slide showing, the children under 6 to 12 is half the adult dose and in children under 2 to 6 is one quarter the adult dose. And then under 2 years of age, right now it says, "ask a doctor or consult a physician." Thank you.

Now, I want to turn the meeting back to the chair.

DR. TINETTI: Thank you very much. We're now going to move on to the presentations by the petitioners and we'll have chance for questions after this group of presentations.

First, will be Dr. Sharfstein, who's the Commissioner of Health for Baltimore City and he'll be talking about overview of the petition. Thank you.

DR. SHARFSTEIN: Thank you very much and good morning. I want to thank the Food and Drug Administration for convening this advisory committee; and particularly, Dr. Schiffenbauer for all his work. I very much want to thank the advisory committees and all the various senior people here taking their time to come talk about this

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issue and also thank everybody else for coming.

I am Josh Sharfstein. I'm a pediatrician and the Commissioner of Health in Baltimore City. One year ago next week nine chiefs of pediatrics in the Baltimore area, the Maryland Chapter of the American Academy of Pediatrics, and the Baltimore City Health Department all joined together to issue an advisory to parents not to use over-the-counter cough and cold medication for children ages 5 and under. The statement was drafted by Dr. Janet Serwint [phonetic] of Johns Hopkins, who would have loved

to be here except that she is in New Zealand.

After we did the statement from nine chiefs of pediatrics, the Maryland Chapter of the Academy of Pediatrics, the most common question that we heard back was, if so many experts are advising against these medications for young children, then why are they so widely marketed and used? And it is true they are widely marketed. In the last fiscal year, from July 1st, 2006 to June 30th, 2007, companies spent more than $51 million advertising over-the-counter pediatric cough and cold medicines. And the themes of this marketing is that the products are safe and effective, that pediatricians

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recommend them and that parents can relax if they're giving the products to their kids.

For example, this is an ad in Parenting Magazine that says, "For babies and big kids, pediatricians recommend PediaCare the most and that makes their moms feel pretty good, too." This ad says, "And just like all our little remedies, cough, cold and fever products, they contain safe, effective, pediatrician-recommended ingredients without additives."

This ad says doctors recommend Dimetapp. This ad in the Women's Day Magazine from November 1st, 2007 says, "Mom worries when a cold makes it hard for her kid to breathe, unless, of course, she has Dimetapp." And this ad from Triaminic Infant Thin Strips, which were marketed with over $2 million in Fiscal Year 2007 says, "Nothing is easier to give your infant to get them bouncing around again than the two new formulas of infant Triaminic thin strips. Triaminic, the medicine of motherhood."

And these products are widely used. According to the Consumer Healthcare Products Association's submission to FDA, about 95 million units of pediatric over-the-counter cough and cold products are sold each

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year. Over a three-year period, they reach 39 percent of households with 44 million buyers.

So coming back again to the question, if so many experts are advising against these medications for young children, why are they so widely marketed and used? And it is our view, the petitioner's view, that there's a gap in federal oversight. That FDA did not approve these

products on the basis of evidence of safety or effectiveness in children. That FDA has permitted widespread marketing that is not supported by the scientific evidence.

And I thought the presentation was very informative, so I will go through this, but basically, about 30 years ago there was a different advisory panel, which was the start of the monograph, and it did find that the evidence in children for these drugs was negligible and nonexistent.

One thing that Marina Chang did not mention is that the panel actually specifically recommended that companies not be allowed to use "infant or baby" in the marketing, although that recommendation was never followed. Since that time, it has been marketed under the

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classification of "generally recognized as safe and effective."

In recent years, however, doctors have reported serious injuries and death in association with these products. Studies have failed to show effectiveness in children and multiple medical authorities have expressed concern, including the American Academy of Pediatrics, the American College of Chest Physicians and the Centers for Disease Control and Prevention. So we think it is very difficult to see how you could classify the products as generally recognized as safe and effective when the profession is so strongly on record.

So our petition is to ask FDA to review the data, which is why we really appreciate this meeting today, to hold these products to an appropriate standard for medicine given to young children. And we believe that over-the-counter cough and cold products for children under age 6 do not meet such a standard.

I want to introduce the other petitioners who are going to be speaking, Dr. Wayne Snodgrass. He's a professor in pediatrics, pharmacology and toxicology at the University of Texas Medical Branch. He's the chair of

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the Committee on Drugs of the American Academy of Pediatrics.

Michael Shannon is a professor of pediatrics at Harvard Medical School, the chair of the Division of

Emergency Medicine at Boston's Children's Hospital and the lead author of the most recent edition of the Clinical Management of Poisoning and Drug Overdose.

And Dr. Dan Levy is the president of the American Academy of Pediatrics, Maryland Chapter. He's a clinical assistant professor at the University of Maryland, in private practice for 30 years and an avid baseball fan.

Dr. Sondgrass, that's me next, and we'll take questions at the end.

DR. SNODGRASS: Good morning. I'd like to share with you a little bit of information in a brief period of time on efficacy and issues about extrapolation.

(Slide)

DR. SNODGRASS: Just an overview of what I'll go over, a bit of data about efficacy or lack of efficacy of these drugs in children and then some of the issues about the risk of extrapolation and adverse effects, and a final comment about some ideas about rational therapeutics.

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Overall, if you look at the data that's available, you would come to the conclusion that these drugs are no more effective than placebo in the relief of cold and cough symptoms in children. And there are data to support that for each of the drugs that are listed that you see there. I will only go through two or three examples of some of the clinical studies that have been published.

(Slide)

DR. SNODGRASS: In this particular study about brompheniramine that also, I believe, included phenylpropoxphene as a combination product. This was a prospective, randomized, double blind placebo-controlled clinical study. This was a number of 59 children and their age ranges were from 6 months to less than 6 years. A 7-point lycord (phonetic) scale was used and this was a short-term, two-hour evaluation.

And that becomes an issue in evaluating the data because a lot of these are parent, not all, but a lot of these are parent evaluations of symptoms. Some, like this study, did it within the timeframe you would expect the short action of some of these drugs. Other did it at 24 or 48 hours, for example. And that pertains to how you

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might assess the design of that trial.

You'll see here, if you look at the symptom and then the drug and then the placebo, in this particular study there was no difference in any of these categories except and you'll see this in other studies as well, the last category asleep, again, is now well known that antihistamines or these the H1 in the first generation cross the blood brain barrier, you get sedative affects and you can see that there was a greater degree of sedation, 46.6, compared to the reported placebo group. Again, these are parent evaluations.

And this other study, this was done in Thailand. It was a prospective randomized, double blind, placebo-controlled trial. In this study the symptoms and rating scales, were done both by parents and physicians. They were blinded to each other's rating scales.

And when that was evaluated, it was found that the physician ratings were very close to the parent ratings. And they used the physician ratings to list their results. Now, I've only listed a very small part that's in this study, but if you'll look at symptom improvement at three days and the rating scale is listed there from a minus one

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to plus three. And they're looking at the difference between their pre- and post-therapy. And you'll see that there's really no significant difference between placebo and drug, except if you look at the sleepiness, which is, again, a suggestion here, as it is in other studies, that there's more sedation with the use of the drug containing an antihistamine in this case. This was chlorpheniramine.

A more recent study by E. N. Paulett [phonetic], Hershey, Pennsylvania published three years ago, is a single-dose study on dextromethorphan, a single dose given 30 minutes before bed. Again, there's a 7-point lycord scale. There were 100 studies, 100 patients or subjects in this study and the age range from 2 to 16 years. And you'll see between diphenhydramine and dextromethrophan these were given as separate agents so again, with the placebo-control. And if you look at cough frequency, was the cough bothersome, the cough severity, parents being the parents themselves, sleeping, you'll see that there's no difference with placebo.

There are a number of other studies that will address efficacy. In your packet you'll see many of those

have been discussed, including some in the Medical

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Officers Review from the FDA, a number of additional studies.

I want to now go to the question of extrapolation because this is really a large part of the basis for the monograph approach is can you extrapolate, and you've just heard weight and maybe height, but certainly weight one fourth, one half, these type of parameters.

When the BPCA Act was passed a few years ago, the Best Practices for Children Act that led to a process where additional drugs were studied in children that hadn't been studied previously. And from that set of data we now have a bit more, quite a bit more of information regarding drugs effects or adverse affects in children that we didn't expect or would not be predictable. And for drugs previously approved for adults, in children we found, for example, some that are ineffective for an indication, Citalopram [phonetic] for migraines, for example.

In that study it was one of the conclusions was that maybe below age 18 that's not a good drug to use for children for that diagnosis. Tolterodine for bladder incontinence did not work. Incorrectly dosed drugs that

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we no work, but the dose wasn't right. Guaifenesin for partial seizures, banasipil [phonetic] for pediatric hypertension.

Sorbitol, although it's not nonprescription, illustrates what pediatricians are often very concerned about. It's not only the kinetics; it's also the dynamics of pharmacodynamics in the response.

And here's an example, out of that kind of data, that below point 3 square meter service area, which is about 6 kilograms approximately, this is a drug that acts as a beta blocker. So it's a developmental receptor response, perhaps. Above that, it's acting mostly is a potassium channel blocker. And in that younger age group, you get more frequent QTC prolongation. And you see there's some correlation with plasma clearance changes and voltmeter distribution changes. So unless you actually get the data, you can't know this information; and particularly, in this case, of course, for a drug that has

a narrow margin of safety.

Extrapolation also applies to clinical scenarios. For example, Fluoxetine, it was found that there is a height decrease in teenagers if you use over a 19-week

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study that was done, a centimeter or less height gain with doses given during that period of time. Fluvoxamine as an anti-depressant, there were differences in dosing need for adolescents and where you might need to actually need to increase the dose compared to what was started with, and in girls 9 to 11 years of age, you may need to decrease the dose.

So those are specifics that you could not predict based on gender or age alone. It was a response. You had to measure the pharmacodynamic response.

Adverse effect issues came up in the BPCA-type of data with Accutane (phonetic), increased bone demineralization, topical pimecrolimus or Elidel this is a topical agent. This is being marketed for just rash in young infants. It's a Sirolimus. It's in the general category of Sirolimus, Cyclosporine and those types of agents, increased infections, fever, diarrhea from a topical agent for that type of an indication. So you have to have data in the age group. And Propofol in recent times increased mortality in multi-day continued infusion in PICU patients particularly.

Where would we go from here? Is it beyond some of

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the considerations that this combined advisory committee meeting? In the future, I think part of this is that you really need to look at the basic pathophysiology cause of the common cold. There are past data published about nasal spray vaccines, concepts about antiviral drugs for some of the viruses that would cause the common cold, intercellular adhesion molecular or receptor antagonists, and the list goes on. But certainly, we need some additional research on the rational basis for therapy in this category of agents. Thank you.

DR. SHARFSTEIN: Dr. Shannon.

DR. SHANNON: Good morning. I greatly appreciate the opportunity to speak with the Pediatric and Nonprescription Drugs Advisory Committees.

As Dr. Sharfstein mentioned, my name is Dr. Michael

Shannon. I'm a pediatrician and toxicologist at Children's Hospital Boston and a professor of pediatrics at Harvard Medical School. I've devoted my last 25 years of pediatric practice to studying the adverse drug events in children, their mechanisms and methods of preventing these adverse events. I was one of the original signers of the March 2007 petition that went to the FDA asking for

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a reevaluation of cough and cold preparation use in children.

And what I would like to do in the next few minutes is to provide an analysis of the risks associated with the use of cough and cold preparations when given to young children.

I'll divide my few words into the following categories. First, I'll briefly provide an overview of the principles of pediatric drug safety and their relevance to cough and cold preparations; the sources of data that keep informing us of the potential risks of these agents; the categories of adverse drug events associated with the use of cough and cold preparations when given to young children and the range of toxicity that's been reported when these agents are given to children.

First, in terms of principles of drug safety, the most important principles are listed here.

(Slide)

MR. SHANNON: First, as Dr. Snodgrass just mentioned, extrapolation of adult data to create pediatric doses is fraught with danger. We have enumerable examples

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of adverse events occurring in children simply because it was felt that, mathematically, one could base a pediatric dose on a child dose.

Second, while passage of the Best Pharmaceuticals for Children's Act and Research Equity Acts have been very important in reducing the risks of adverse health events in children. They have only begun to correct an enormous problem. That is, that 80 percent of the drugs given to children have not been adequately tested in children for safety and efficacy. We do believe the time is now for the FDA to begin evaluating agents, particularly those that were previously designated as generally regarded as

safe and effective.

(Slide)

DR. SHANNON: The documentation of adverse events is found in multiple sources of data, the most important of which are listed here. I do want to emphasis that despite this broad range of data sources, many adverse events from cough and cold preparations are under reported, unpublicized, and unrecognized.

You've seen these data, so I'll be brief. First, a recent review of five years of data from national poison

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control centers reported more than 325,000 calls to poison centers about children who were exposed to cough and cold preparations. These calls were not only about overdoses of these agents, but they also represented drug interactions and other unexpected toxicities; and there were 12 deaths in that series.

The two papers from medical examiners offices I've listed here have attributed 18 deaths to cough and cold preparations given to young children. There are more than ten published reports of toxicity from cough and cold preparation use when given to young children with several fatalities. The adverse events associated with these agents are broad ranging and include hallucinations, agitation, seizures and cardiac arrest.

Finally, the FDA, the CDC and other public health authorities have reported adverse events when cough and cold preparations are used in young children. The FDA, in their 27-year analysis of adverse event reporting system, identified 401 serious adverse events and 123 deaths. In a paper in the MMDR in January of this year, the CDC reviewed three infant deaths in two states.

In that paper, the CDC estimated that over a

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two-year period, 1,519 children were seen in emergency departments for evaluation after known or possible exposure to cough and cold preparations.

And then, finally, at a more local level, there have been 900 calls about children under the age of five in one year reported to the Maryland Poison Control Center and four deaths in children under 4 reported from Baltimore.

It would be a mistake that that sole problem with cough and cold preparations is overdose and therefore

poison prevention efforts would solve all the risks from these drugs. Rather, there are multiple categories of adverse drug events that can occur. Acute single overdose is certainly more common, the result of the curious toddler or the well-intentioned parent who makes a dosing error. However, even when the parent follows dosing guidelines, children with altered drug kinetics can develop chronic over medication with disastrous consequences.

Finally, in what we call therapeutic misadventures, parents may give these preparations to a child who has significant underlying illness or who is taking another medication that will interact with cough and cold

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preparations. Collectively, these three potential mechanisms of poisoning form a constant threat to children given these medications.

Reported adverse events from cough and cold preparations when given to young children involve a range of organ systems, cardiovascular systems is the most common and the range of effects you see listed here ranging from high blood pressure, tachyrhythmia, cardiomyopathy, and cardiac arrest. Neurologic events include neuro-behavior events such as hallucination, agitation, psychosis or frank seizures. Metabolic acidosis can occur from mechanisms that are unclear, probably just from added physiologic stress on susceptible children.

And then, finally, many cases of adverse events or even fatalities were uncertain what the mechanism of toxicity was.

I'd like to close by emphasizing the following principle. When a treatment is ineffective, its risk, if not zero, will always exceed its benefits. Cough and cold preparations pose genuine risks when given to children under the age of 6 with no associated benefit. We believe

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that available safety and efficacy data provide compelling evidence that if we believe in this principle these agents should not be used in young children. Thank you. I look forward to addressing your questions.

DR. SHARFSTEIN: Dr. Levy. While he's coming up, I'll just mention that we did distribute a breakdown of

the adverse events, both by under age 2 and in the 2 to 6 group for the Advisory Committee.

DR. LEVY: As a baseball fan, I was very thrilled to be selected as the pediatrician for the 1993 baseball all-star game in Baltimore. And so I thought I was pretty hot stuff and I introduced myself to Roland Heiman (phonetic), who at that time was the general manager of the Orioles. I said Mr. Heiman, I'm the pediatrician for today's game and he said, great, because I'm having terrible problems with my feet.

[Laughter]

DR. LEVY: It's my privilege to be here as a child advocate. And it's my privilege to speak to this argus body because I'm a pediatrician and I've been in practice for 30 years. So I've been on the front lines and I've had to deal with the consequences that we're trying to

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talk about today and hopefully, change it.

And I'd like to present a couple of cases that have come to my office in the past week, which are emblematic of the kinds of things that pediatricians are dealing with on the front line.

The first case is of a young child, an 18-month-old, who came into my office this past week and the mother said that she had been coughing for over a week. And for the past three days prior to her calling me she had been administering medication, a dose of over-the-counter cold medication.

So after administering this medication, which I did not advise her to use. She simply used it on her own. She then was calling me to be sure she was using the right dose and what she should do. At that point, I said, please, come to my office. We made an appointment, and when I examined her I found that the child was wheezing. And when she was treated with appropriate doses of medication for asthma, the cough immediately resolved.

Where did she get this information? Well, you need to know that greater than 50 percent of the national body of the American Academy of Pediatrics, that's 62,000

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members greater than 50 percent of our membership is under the age of 40. So obviously, I'm one of the old guys. I submit to you that there isn't a responsible

pediatric training program in this country that teaches its residents to use any kind of cough or cold preparation.

I learned 30 years ago at Children's Hospital in Philadelphia that these medicines didn't work and I think we've accumulated more information since then to support that. So the two things that are particularly objectionable to me as a pediatrician in practice, on the front lines are that the preparations are advertised in all kinds of media to vulnerable people who are worried about their children that it's pediatrician recommended, and then they should call their pediatrician to get the appropriate dosing.

Well, if we're dealing the appropriate dosing on extrapolated data from adults with medications that have never proven adequately to be tested in children, we have a problem.

The second case that I'd like to present to you is even more serious because it underscores another problem

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that we're having in practice and that is that a child came to me, a 3-year-old, who, again, had been treated with cold medications at home for several days because he had fever, worsening cough and was looking pretty ill. He visited one of these little patient first retail clinic-type places, was told to continue to use the cold medicine. That everything was wrong.

The parent called me after the child had been sick for a week came to me and I found that the child had a low-bar pneumonia and we needed hospitalize him for treatment of this very serious, life-threatening bacterial illness.

Now, what are we supposed to do out here? We're being asked to give advice on preparations that most of us don't recommend and so where are people getting the advice to use these medications? They're getting it from the media. And the media is, unfortunately, just a vehicle for companies who want to sell a product. The product is not being sold so much for its benefits really as its being sold because it's being connected to an emotion. And the emotion that we're dealing with in pediatric practice is fear and vulnerability and caring. So these

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are parents who think that they're doing the right thing by giving these medications and unfortunately, what happens is that we, as pediatricians, have to end up facing the consequences.

How do I advise parents to dose these medications? I ask them to unscrew the top of the bottle and in one easy motion invert over the toilet and I tell them that the medication will probably administering it that way the medication will then do more good in curing that child than if it was administered by mouth.

So do understand, and what hasn't been addressed here is, that parents administer these medicines, A, because they're busy and they've got to get to work; B, because they think they're going to make their child better and that it's going to cure the cold or cure the cough; and C, because they don't want to bother us, particularly, at 2 o'clock in the morning, and none of the above are true.

We want to hear from these parents. We want to help them, and we want to do the right thing, and so that's why we are here as pediatricians today, why I'm here representing the pediatricians of my state and the

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American Academy of Pediatrics.

We would like the FDA to look at how these products are being marketed. We would like to make sure that these medications that you take a hard look at these medications and see if they are truly safe and efficacious, and understand the vulnerabilities of the public, the consuming public in using these medications and the problems that using these medications present to us in terms of delay in diagnosis and the delay in the administration of proper care to our patients. Thank you very much.

MR. SHARFSTEIN: I'm just going to briefly close with a go back to what we were asking for in the petition. First, that the FDA provide a statement to the public explaining that the over-the-counter cough and cold medicines have not been shown to be safe and effective for the treatment of cough and cold in children under 6 years of age.

Why is a statement from the FDA so important? We think that it is very important now to counter misleading

information. The Consumer Healthcare Products Association repeatedly states that the products are safe and

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effective, beneficial in relieving symptoms in a recent article in our hometown paper in Baltimore and also that the label clearly spells out what a medicine is for, what active ingredients are there, how much and how often it should be taken.

It's just not true for a lot of the doses that have been there. And even last week, these medicines are safe and effective when used as directed. That is the message that is still being sent. It's very important, we think, for FDA to be clear on the state of the scientific evidence for the public.

Second, we request that the FDA notify manufacturers of products whose labeling uses terms like "infant, baby, toddler" and displays images of children under the age of 6 that such marketing is not supported by scientific evidence and could be subject to enforcement action at any time.

And third, that the labeling be amended to clearly state that the products have not been found to be safe or effective in children under 6 for treatment of cough and cold, and they should not be used for treatment of cough and cold in children under 6 years of age. Thank you very

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much. We're happy to take questions from the committees.

DR. TINETTI: Thank you very much. We'll open up for questions. Before we do that, I might want to remind Dr. Levy, at least in some areas, it's illegal to dump medications that might be considered toxic in toilets. So you may want to recommend that they bring them to their toxic center.

[Laughter]

DR. TINETTI: So we'll now open the panel for questions for any of the speakers today, and just remind you to use your "talk" button and then it off when you're done and to identify yourself for the transcriptionist when you do speak. And just raise your hand and Darrell will record your names and call out when it's time for you to ask your question.

MR. HENNESSY: Thank you. Sean Hennessy. The recommendation that you are making is for children under

the age of 6. I'm wondering how you arrived at that cut point. From reading through the packet, it looks like there aren't data suggesting efficacy in children under 12. So what are you recommending between ages 6 and 12? And then, are there data showing efficacy over the age of

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DR. SHARFSTEIN: To my knowledge, there are no good data showing efficacy in children over the age of 12. The age of 6 was chosen because that's where much of the data is. But if you look carefully in a study or two I showed and also in the FDA review, for example, which does collate a fair bit of that literature, that you'll see there are a number of children up to ages mid-teens and it's not been shown to be effective.

DR. SNODGRASS: I'll add, I think, one of the factors for picking six for the petition was the urgency that we feel for that group because of the frequency of the adverse event reports and the concentration there under age 6 that we feel that that's a more urgent issue to be addressed. But it's not to say that the petitioners have concluded that it is safe for older kids.

DR. PARKER: I have a question, clinical and then regulatory, and I'd like to sort of hear a clarification to help me think about this. When I think about having a cold, I think about congestion, cough. I also am trying to think of what the average person thinks, and I often think of fever. You know, it's not always there, but it's

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often there and then some of what we clinically, as physicians, might label you know, maybe their malaise, maybe their aches and pains, and so, clinically, I would put in the diagnostic criteria fever, aches and pains. And then I'm looking at the active ingredients in cough and cold preparations and I'm trying to figure out what to do with acetaminophen. It's not listed officially as an active ingredient, yet in the dosing comes into play with various dosing recommendations for that when you do combinations versus the other active ingredients that are on the official list.

So I'm looking for clarification, clinically, on whether or not we put in the symptom list fever, aches and pains; and then therapeutically with that, we put I saw

the term "internal analgesics." I'm also wondering about antipyretic as an active ingredient in the treatment of cough and colds and how this plays out in the combination therapy with dosing down the line. So I'm looking for guidance, clinically, clarity clinically, whether or not its in the list and we consider it in the list from a therapeutic standpoint and then from a regulatory standpoint how that category of drugs I'm sort of

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assuming it's in there in my question, but I'm just looking for clarity.

DR. SHARFSTEIN: Now, I think from the petitioners' point of view our petition does not cover acetaminophen, ibuprofen alone. And I'll defer to FDA, but I don't think those are covered by this particular monograph either. I'll defer to FDA. I don't know, Dr. Snodgrass, if you want to discuss that. It's certainly not in the petition.

DR. SNODGRASS: Well, I would certainly say, for me, this is why you need single ingredient products, very clear, and that's the only way you can fix dose combinations. You have no way of adjusting dose to treat the individual. The first principle of therapeutics is individualized therapy and you can't do it with a fixed product combination.

DR. PARKER: Dr. Tinelli, did someone from the FDA want to address that point? If it's not actually part of the monograph, can it be addressed in terms of the combinations?

DR. SNODGRASS: Yes, when the panel looked at these products, this was a permitted combination even though the

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internal analgesics were not included in this particular monograph for cough and colds. So it is a permitted combination to add into it. But it falls under acetaminophen is marketed under the monograph. Ibuprofen currently is marketed under new drug applications. Okay.

DR. TINETTI: Dr. D'Augustino.

DR. D'AUGUSTINO: I want to thank the FDA and the petitioners for their presentation. I've lived through an awful lot of the FDA activities and it was great to hear a summary of it.

My question is to the petitioners. I'd really like

to get a context for myself in terms of what it is that you're saying in terms of the efficacy and the safety. I mean one could argue that the efficacy is because the efficacy hasn't been shown because they just don't run large enough studies in children and so should we be running large studies or do you think there is no efficacy in terms of the date?

And in the safety, you said it isn't overuse, but then the list of overuse, chronic over medication and interactions has the flavor of at least the first two were overuse and the interactions are things that, again, need

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to be investigated at any level. So are you calling attention to the fact that we have children that are being over medicated or what have you and we think that there's no efficacy and we think that there's tremendous safety issues or is it an investigation where we really need to pin down are they safe and are they effective? And if they are safe, in what ways do we instruct people because we all have a lot of friends or whatever and when they call up their pediatricians, the pediatricians tell them to take the drugs.

And I mean, it's also the pediatricians that are somewhat at fault in terms of how this is playing out and I really want to get a sense of where the petitioners are coming from. Thank you.

DR. SNODGRASS: In the November 2006 issue of Clinical Pediatrics, you'll find a study out of Sick Kids Hospital in Toronto. Fourteen percent of Canadian pediatricians would have recommended a cough and cold medicine for ages 6 months to 12 months. Now that's an education issue, and a greater percentage of family practitioners. So that is part of the problem here.

Efficacy, from a clinical perspective, we have

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multiple studies that show no efficacy as done under the conditions of those studies, which, I think from a pediatrician's point of view, would be clinically relevant. You can make the case that how those outcomes were measured, the timing, for example, things like that. Certainly, better studies can be done. More studies can be done and it may well be that with appropriate studies in the future some degree of efficacy can be found.

That's going to have to be correlated with much better dose response information. Then we'll relate to safety eventually as well. So there is a need for future studies, but currently under clinical conditions they're just not efficacious.

DR. D'AUGUSTINO: I'm trying to get, and you're answering it. I mean is there a feeling on the part of the petitioners that these drugs aren't effective or is it they just haven't been studied to show effectiveness?

DR. SNODGRASS: It's not just a feeling. I only presented a couple or three two or three studies. There are other studies that will show you there is efficacy as done by randomized controlled, placebo-controlled, double-blinded clinical trials. So I think the data is

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there for that.

DR. D'AUGUSTINO: Thank you.

DR. SNODGRASS: I'd just like to make a couple of points. A statistician or methodologist will tell you that no study is perfect and there are very few adequately powered studies to definitively answer a question. So what we do, and it has served us well, is to rely on the preponderance of evidence. And the preponderance of evidence that we currently have as we sit here now is that these agents are not effective in young children.

And then, in terms of safety, I'll just reiterate what I said earlier, which is that, again, while acute single overdose is the most common situation, the most common cause of adverse events to young children, it's only a portion and I emphasize that because I know that many believe we can use what the poison prevention strategies that have served us well over the years to prevent these overdoses and keep adverse events from occurring, but that would still leave the category of children where dosing guidelines are absolutely correct, everything should be going well, but because it's a young child or the child has taken a medication or because of

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the child's underlying illness an untoward event occurs.

And I just feel forced to go back to my last slide, which again, just says that when a treatment is ineffective, its risk, unless there's zero, will always exceed its benefits and it should not be made available.

It should not be a therapy.

MR. LYONS: So the idea is just to wait out the cold?

DR. SHANNON: Absolutely.

MS. TINETTI: Thank you. Dr. Rappley.

DR. RAPPLEY: My question follows on your last comment there, Dr. D'Augustino. I understand that the petitioners strongly believe, and provide evidence, that these medications are not efficacious under any circumstances. But I'd like to ask a slightly different question. Are there adverse outcomes to not treating cold, rhinitis, including discomfort, impairment of daily activities, which would apply to an infant as well as a parent?

So I'm not asking you about these particular medications. I'm asking you are there studies about the adverse outcomes associated with these conditions?

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DR. LEVY: Well, I'm here as the humble pediatrician, so I will defer to my academic colleagues on the actual studies. Although I will say to you that it's extremely important for us to be able to, first of all, present the best advice to our patients and the advice that's best based on evidence. I think that's our fiduciary responsibility and that's what a lot of these hearings are about.

The second thing I need to say from a clearly clinical standpoint, addressing your question, is that in the long run what I will say to my patients, and this is again evidenced-based, is that the less you do for the common cold the quicker it gets better. If there are bacterial complications such as altitus [phonetic] media, sinus infections or something more serious, of course, we're going to treat that. But we know that if we're drying up nasal secretions that are laden with white cells and with immunoglobulin and all these wonderful things that protect the child, we actually may prolong the course of that illness and make it a longer period for the child to get back to school and for the parent to get back to work. We will now present more evidence.

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DR. SNODGRASS: The common cold is self-limiting, and in those proportion of emphasis it will go on to more

serious bacterial illness, these medication won't prevent that.

MS. TINETTI: Thank you. Next, Dr. Gorman.

DR. GORMAN: Is it the petitioners' intent to limit the availability of these chemical maleates or only limit the availability of these chemical maleates for this particular indication of cough and colds? In other words, would Dr. Snodgrass or Dr. Shannon be willing to venture that some of these agents, at some dose, are efficacious for some condition, be it not cough and cold?

DR. SHARFSTEIN: I'll let them speak. I'll just say from strictly the petition, it is about for this use. That's what the petition covers, and one thing that we want to be clear about because this question has come up. We're not covering, for example, antihistamines alone for allergies. So some of these products may be in cough and cold medicines, marketed for cough and cold and also marketed for allergy alone. Our petition does not cover the allergy part of it.

DR. SHANNON: I would say that for each of these

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agents, singly, we know they have pharmacological effects, which have the potential to be beneficial in certain host. The ultimate question, though two questions are, one, what is the therapeutic index, what is the difference between the therapeutic dose and toxic dose for these agents? And number two, are they effective for cough and cold preparations. And again, we believe that the answer to the latter question is no.

DR. TINETTI: Dr. Goldstein.

DR. GOLDSTEIN: The skill and dedication of the speakers are beyond question. As I'm sure Dr. Levy knows, Jacques Barzon [phonetic] once said that those who wish to know the heart and mind of America must learn baseball, so you're to be commended, Doctor, and I share your passion, by the way.

But I'm puzzled about one thing and would ask the speakers to address this. If these medicines are allegedly not effective or materially unsafe, how is the purchase of millions, hundreds of millions of doses by parents explained? It is these days, perhaps, simple to lay the onus upon the media or advertising. But I don't believe the American caregiver or parent is, in a word,

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stupid. They buy and they repurchase it and they are able to recognize in most case symptomatic relief. Are we saying, in effect, that they're going to spend the money anyway whether they don't get the relief or not simply because somebody told them to or put a pretty picture on a box? I don't think so.

DR. SHARFSTEIN: I'll give an answer to that and then I'll see whether the other petitioners want to add. I don't think this is about parents. I think it speaks to why clinical trials are done at all. I mean people are going to find improvement when the condition is actually self-limiting. But I think it speaks to clinical trials, generally, because parents when it's in the market with advertising and the fact that it's a self-limited illness and the kids are getting better anyway may say that they think the product's contributed to that, but the same parents in a clinical trial when they're giving either the drug or a placebo, those same parents can't tell the difference between them. They're reporting the same levels of symptoms.

So it really speaks to just, generally, the question of why do randomized-controlled trials, because there are

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many examples of things in medicine where doctors, including some of the most experience doctors would think that something would work, would be sure that something would work and then when you do the trial you don't see it. And in this case, parents, themselves, in a clinical trial situation, aren't able to see the benefit.

DR. SHANNON: The analogy that comes to my mind is the story of Ipecac. If you'll remember, after the FDA permitted over-the-counter sale of Ipecac in 1966, for the next 40 years, at pediatricians urging, but also as a result of marketing, felt it important to place it in every home and give it for every poisoning and pediatricians as well as parents completely convinced that was true until the preponderance of data showed that not only was Ipecac ineffective, but was associated with harm. And at that point, which was now two years ago, the American Academy of Pediatrics completely withdrew its support for the use of Ipecac. We made a mistake. Mistakes are made in terms of examining the safety and

efficacy of products. But when the preponderance of data presents themselves in such a way, we have to accept those data and make an action.

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DR. LEVY: No, people are not stupid. However, I think that people need to get back to work. They are interested in quick results. As I said during my remarks, I think that it's the general consensus amongst parents, if you were to ask them, that most of them think that administering these medications will make their children well and will hasten their return to their normal life, and I think that's where we're coming from. People need and want quick results. This is the era where when we're IMing each other and we are sending messages by computer and we expect that we're not going to wait more than 15 seconds for an answer and this is the atmosphere in which pediatricians and others who are concerned about the health of children are practicing these days. We have to deal with the pressures from the consumer market. It's not simply a matter of the media conveying a certain message. It's the way things are in society today.

DR. TINETTI: Dr. Daum.

DR. DAUM: Thank you. I'd just like to build a little bit on a question. I think it was the very first one that was asked, and here a comment briefly about it. And that is that 6 appears to have been chosen relatively

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6 years of age appears to have been chosen relatively arbitrarily and supposing we looked down the road and there is some movement to agree with the petition and these products should no longer be sold, et cetera that outcome. Isn't there a tacit endorsement that, with the recommendation that seven are older it is safe and effective? And I'm a little concerned about that cut off and sort of how to think about the difference between a 6-year-old and a 7-year-old child and this very issue we're discussing.

DR. SNODGRASS: I'm going to just speak for myself. Yes, I think there could be a tacit endorsement. I think the data are that I'm aware of is that there's not been efficacy shown in older children as well as younger. That's just what the data are.

DR. DAUM: But then why 6?

DR. SNODGRASS: Well, I think Dr. Sharfstein explained that was the original version of the petition simply because we thought that was kind of the most urgent group where there have been some overdoses, where there have been some deaths. That was largely the reason.

DR. DAUM: Can I follow up with one more thing? Do

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you think that there are, and this may be outside the scope, and the Chairman may tell me to be quiet, but do you think that there are sufficient data in children over 6 or that we should think about whether additional studies are needed in that age group? Or do you think the data in children over 6 are as compelling as the data we're being asked to consider today?

DR. SNODGRASS: There may not be as much data, although there are several of the studies, if you'll look through the materials you have, that clearly they're over the age of 6 and not showing any benefit and not showing any efficacy. Are they as compelling? Perhaps, because the numbers may be somewhat less, might be less compelling. But otherwise, I think they're relatively compelling as far as efficacy as they are currently marketed, efficacy as they are currently being dosed and by the way they were evaluated in those randomized studies. That doesn't preclude that in the future individual pharmaceutical companies could do further studies to try to show efficacy.

DR. TINETTI: Dr. Cnaan.

DR. CNAAN: I actually had a question for Dr. Chang.

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In the work from 30 years ago, about a hundred of 800 ingredients were classified. My two questions are what happened to the 700? What is their regulatory status? And my second question is that was 30 years ago. How many different ingredients are there approximately today?

DR. CHANG: The 800 I talk about is inclusive for the OTC product. It's not just a cough and cold. So for the cough and cold panel, they looked at, for the four categories that we looked at, there were a total of 92 ingredients. Okay. And for today, you remember in my slide on the right-hand column I had 35 make it to the final rule and in your package, part B, section 1, tab 3 you have a list of all the active monograph ingredients.

I'm not talking about the NDA ingredients. So the monograph ingredients you have a listing. It's a total of 35, which include oral and topicals.

DR. CNAAN: So in other words, beyond the 92 that were classified as either 35 or others, there are no new ingredients for cough and cold since then.

DR. CHANG: The monograph process is a little bit different. Okay. Unless the product has been on the market for a long time and then people will petition to

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ask to put it in the monograph. See, it's different than NDA. NDAs, the manufacturers submit it for the specific products and NDA will submit an application and we review it, and then they're the only sole marketer for certain, you now, three years or whatever, five years. Then a generic version can come in as an ANDA. But the monograph is once someone petition us and we go through the rulemaking process and allow it to be on the monograph, then anybody can market it. So there's no pre-requirement for FDA. But since the review, we have not received any new petitions to put more ingredients into the OTC cough/cold monographs.

DR. TINETTI: Dr. Joad.

DR. JOAD: Yes, this question is for the petitioners. The extrapolation argument suggests that these preparations work for anybody and my question is my understanding from the Cochran metal analysis is that they weren't able to show efficacy for anyone and my question is do you think it works for anyone, adults specifically?

DR. SONDGRASS: There is in the Cochran analysis for pseudophedrine in adults a 6 percent benefit for the common cold. Whether that's clinically significant is a

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different judgment, but could be demonstrated by the data in a statistical manner a 6 percent benefit for adults the one agent for cold, beyond that, no.

DR. SHARFSTEIN: I'd just say this relates to the other question insofar as the petition focus on the under 6 and we didn't try to swallow the whole think in one petition. And I think we realize that the petition itself would raise these bigger questions, although I think it requires an advisory committee and the FDA experts to really answer the questions beyond the under 6 population.

I think we feel the urgency there because of the number of injuries that effects at a public health level as well as a clinical level as well as at an expert level that's why we focused there, and however it works out, we're very focused on making sure that that problem gets solved because we think if it doesn't there will be products that continue to be marketed saying "pediatrician recommended" when we think that they really do pose a threat without evidence of effectiveness.

DR. RAPPLEY: As we think about this concept of preponderance of evidence and the risk benefit ratio to the decision to treat, I would like the petitioners to

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reflect on the relative roles for parent, physician and government in weighing in on that preponderance of evidence.

DR. SHARPSTEIN: I'm going to let the experts talk about it, but I would say, just right off, I think it's not just parents, physicians and government that are there. You have to think about the companies making the products because they have a $50 million voice in it, and as you're thinking of what the roles are it's not like it's an abstract question. The government's role is important because there's another voice that is a very important voice in how the products are used and marketed.

DR. RAPPLEY: I'm not thinking so much about the things that influence our decisions, but what we are talking about here in many ways is access to these medications and so should the decision about the preponderance of evidence lay primarily with the government in making them difficult to access or perhaps indicating they should never be used. Should it be the gateway at the physician and with their body of knowledge and their experience be the one to judge the preponderance of evidence or should it be at the level of the parent and

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implies a different ability or a different set of information then by which one weighs the treatment decision?

DR. SNODGRASS: I'm just making the point that that is not a kind of neutral kind of weighing because part of the issue is what degree of advertising and marketing is permit to affect that decision. I think that plays an

important role.

My view is that if a product is not safe or effective there's nothing that a physician or a parent is going to do unless they have magical powers to make it safe and effective, and that's really when the evidence is really clear that's where it's very important for the government to be clear about it. Otherwise, you wind up with children, at the end of the day, getting unnecessarily injured.

DR. SHARFSTEIN: Perhaps part of the consideration, in answer to your question, is usage studies for products that might go over the counter and are persons, general persons, parents, are they able to discriminate and make decisions? And a number of those studies in a variety of areas are showing there is always some group that can't.

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So here you have a situation of there's no efficacy. There are some adverse affects and adverse risks, and to leave that to parents, I think, is unfair to children and parents. That's a personal opinion.

Now, should the government or should it be a physician as a gatekeeper? Physicians, at least some percent of us, need some education to not recommend something that's not effective. So how good a gatekeeper would that would it be a burden? Would it be an unnecessary burden? I don't know. But I think on some level you may want to distinguish efficacy and safety, the degree of that, and it probably in this instance becomes an issue for the government to take some action.

DR. TINETTI: Thank you. I think my question is actually going to be quite related to that. I was sort of struck by the fact that and I agree with you it has to be a safety and effectiveness sort of balance issue. I was sort of struck by the fact, however, that as petitioners you're sort of relying on a few small, randomized-controlled trials to show lack of effectiveness and ignoring the fact that millions and millions of people are using these and are voting with their pocketbook and

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even informed people who don't necessarily get their information from the media. And clearly, they feel that they are effective or they wouldn't be using them. And you seem to be disregarding that level of evidence.

On the safety side of it, certainly, one death and adverse effect in a child is horrible and terrible. But on the other hand, if you look at the data that you've used, it's from a few poison control centers, a relatively small number of case studies over millions and millions of uses and so certainly one can argue that there may be a wealth of evidence of effectiveness that you're disregarding and we have little sort of systematic evidence on the frequency of the adverse effects. And I wondered if you would respond to that.

DR. SNODGRASS: If there's a wealth of evidence, I'd like to see it. It is Cochran Level 1-A or is Cochran Level 4-D? I mean those are the things we can ask about.

DR. TINETTI: I'm talking about the evidence of the fact that people themselves are using these products that feel that they are beneficial or they wouldn't be using them.

DR. SNODGRASS: Sure. Of course, I think the

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experiment to be done is very simple. You keep the products out their with the same label on them and you just put saline in there. And you will get what we already know from the studies; you'll get some benefit as said by the parents.

The safety issue Dr. Shannon can address better than I. The question is how many children do you want to die is the way pediatricians would look at it. If we got the chance to really eliminate even one or two deaths, that's worth the effort.

DR. SHARFSTEIN: Let me just add the history of the FDA itself there's so many examples of products that were widely used by parents and physicians that when they were adequately studied did not prove to be effective or safe, and that's one of the reasons the agency exists is the idea that you just can't trust what doctors or patients will do on their own in the absence of good, clinical data.

DR. TINETTI: But we have to weigh that against the fact that we're hearing that this may be not an easy thing to get good, clinical data. So I think at least it's important to keep that perspective.

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DR. SHANNON: True. But I would, again, emphasize

that the number of adverse events that we reported, one, are an underestimate, clearly an underestimate, but again, because of a lack of reporting and lack of even recognition. And so while the number I presented to you is a small number based on the millions of doses used are relatively large number when one thinks this might be the tip of the iceberg.

Regardless of that, I still think, and my argument would be, that if it's ineffective, if they really have no effectiveness, then even one adverse event means that the risk have exceeded the benefits, even one.

DR. TINETTI: Dr. Calhoun.

DR. CALHOUN: Thank you. I'd actually like to come back to this matter of efficacy with the aphorism that the lack of evidence is not evidence of lack of effect. And so the question is that the outcome measures that were reported in those trials are actually pretty blunt tools and is it the position of the petitioners that there is absolutely no efficacy, even with a perfectly designed trial, even with good, clinical trial tools that there would be no efficacy? Or is it the position of the

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petitioners that the blunt instruments that have been used in the trials to date have not been able to resolve benefit? I have a related question after you've answered.

DR. SNODGRASS: My perspective would be that it's not quite so blunt an instrument because it's relevant to clinical practice as those studies were done. They were done under those conditions. So it is still common practice to ask the parent how the child is doing or maybe a physician on a clinical level. So in that sense the discriminatory value of those outcome measure was, I think, quite applicable and we have reproducible data from different studies of the same final result. Could there be efficacy? Yes, I think if there were what I'll use the word "carefully done future studies" it's been pointed out by others that cough, for example, it could be an objective finding. You could do tape recording as was done many years ago in a study. It was simply that particular study was not blinded. So you need all the high quality characteristics of a very careful science study. Yes, you may well find efficacy.

The issue about children is different than adults

would have to come into play in this. You'll hear about

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airway diameter differences, lung growth occurs through age eight or nine. There are probably unknown differences with regard to cholinergic responses. Certainly, children with larger cholinergic tone, rhinitis is more of a cholinergic phenomenon. So I think if it's carefully done and you evaluate its time course do you give the dose, when do you evaluate those types of things, very carefully conceived studies may very well show some efficacy. They don't exist and until they exist should we have drugs available under this condition to use. The dose is out there. Think about the doses. What are the does that are available right now? Where do they come from?

There's an old study on brompheniramine getting as somewhat the minimum effective dose, but what's the variation in the next 100 2-year-olds or the next 100 6-year-olds? The difference in the physiologist and the pharmacologist is the pharmacologist uses more than one dose, and you have to do response and that's missing.

DR. SNODGRASS: I just want to say to go back to a point that Dr. Levy made, let's say you're going t think about what studies in the future could be done on these

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products. The study that I think is important from a public health perspective, given that the common cold is not very morbid, ultimately in kids, is are these products keeping parents from pursuing treatment that's necessary for more serious conditions? It's broader than just if you find the child that you know has the common cold, could you figure out a study that could count the coughs and they're a few less.

But how confident are we that we're not missing that kids aren't suffering and getting into trouble with asthma and pneumonia at home because the parents are dosing these products at home. It's a type of extrapolation risk that is very important, I think, for the committee to consider that when you're extrapolating from adults to kids you don't necessarily know how the product would be used in kids and whether you're covering up conditions that are potentially interfering with the important care that needs to be given for conditions that are very serious in

children.
DR. TINETTI: Thank you. I think we're getting up on our break time. I think we'll take one more question now and there will be time this afternoon for all the

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questions we don't get to. So there will be plenty of time for questions. Dr. Parker.
DR. PARKER: This is again just so I'm clear on this. From the petitioners' standpoint, there's no safe and effective therapy for cough and cold.
DR. SHARFSTEIN: I think what we're saying is that none of these products that are marketed now are safe or effective.
DR. PARKER: Okay. I'm a clarity person, so sorry to slow this down a minute -- antihistamines, anti-bronchial dilators, expectorant, nasal decongestants.
DR. SHARFSTEIN: That's correct.
DR. PARKER: That five category.
DR. SHARFSTEIN: Correct.
DR. PARKER: Are there safe and effective therapies for the common cold?
DR. SHARFSTEIN: Love.
DR. PARKER: I'm serious.
DR. SHARFSTEIN: This is what I recommend to kids.
DR. PARKER: This is important. The reason I'm asking this is this gets into label clarity for the internal analgesics. And so that's where I'm going with

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this. So I'm looking for clarity form you all so that I understand this.
DR. SHARFSTEIN: I think there's a question of relief from pain and fever that's totally separate from this petition. But I'll let Dr. Snodgrass .
DR. SNODGRASS: Specific therapy for the common cold, no. It's nasal bulb suction, saline nose drops that type of thing. But if you're having discomfort, you have an associated pain, as an example, then we know acetaminophen can be beneficial, ibuprofen can be beneficial. It's back to single ingredient that type of questions. So those would be symptom treatments if you had that expressed. But for these products for the common cold, as has been measured in these studies, no.
DR. PARKER: Are there other products you'd put on

that list for the common cold and therapy of the common cold because those are covered under another monograph when I asked that earlier, yet they relate to symptom relief for this clinical condition and I'm just trying to figure out how we make sure the therapeutic decisions and how we educate the public through marketing of products and educational efforts on the part of people who are

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trying to provide good care for the public -- how we make sure we're clear on what the goal is here.

DR. SNODGRASS: I can think of none that are in categories that are currently marketed the immune stimulators and modifiers, nothing, no.

DR. TINETTI: Dr. D'Augustino, is your question very short or can we hold it until this afternoon?

DR. D'AUGUSTINO: Very short.

DR. TINETTI: And the answer very short, also.

DR. D'AUGUSTINO: Well, there may not need to be an answer. The cough/cold I mean there have been a lot of studies on cough/cold and so forth. And if you wait five days, the cold goes away. And so addressing the cold is oftentimes addressing the particular symptoms and there's a lot of, I think, positive studies, which we don't want to leave the table or start the break thinking that there is no evidence that cough/cold preparations work. And that's more of a statement than it is a question.

DR. SHANNON: I have just one comment just to go back to your question. Again, we are placing acetaminophen and ibuprofen out of this category because those are medications that have been well studied in

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children and we know that they have efficacy and we know that they have a wide safety margin when used properly. Those are two agents not part of this petition.

DR. TINETTI: Thank you very much. We're going to come back in 15 minutes and just remind the committee nobody should be discussing anything about the presentations. Thank you.

(Recess)

DR. TINETTI: I'm going to ask everyone to take their seats. We're going to start the next part of the meeting. Thank you.

We're now going to be hearing from the industry

representatives, and the first speaker will be Linda Suydam who is the president of the Consumer Healthcare Products Association.

DR. SUYDAM: Thank you. Good morning. I'm Linda Suydam, President of the Consumer Healthcare Products Association or CHPA. On behalf of the leading makers of pediatric over-the-counter cough and cold medicines, I'd like to thank the FDA, the members of the Nonprescription Drugs and Pediatric Advisory Committees as well as the authors of the Baltimore Citizens Petition for raising the

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critical issues we are discussing today.

The safety and safe use of our medicines are our top priority, and the harm of any child associated with any of our medicines is of great concern. It is important, however, to truly understand the cause of harm as well as what the best course of action is to address it.

To that end, we recruited independent, outside experts to review relevant data related to the safety and efficacy of cough and cold medicines, and we will share their findings with you today. And from these findings, we've developed a very robust and targeted plan specifically designed to improve the safety and efficacy of these medicines.

We welcome this opportunity for public review of the scientific data and look forward to a frank and open discussion. We see the next two days as an opportunity to get your input on our recommendations and plans because while we may disagree on some things all of us here share the same goal, safe and effective over-the-counter medications for children.

Here is a brief overview of what you will see and hear from us today. I will begin by putting these

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medicines in context and introducing some of the industry's top line recommendations for new labeling, scientific studies and educational programs. We will then explain the data and information that lead to these recommendations. This will include background on efficacy research in pediatric populations for OTC medicines, how pharmacokinetics or pK data allow us to bridge from adult efficacy and a review of both industry and independent analyses of a number of safety databases.

Finally, I will wrap up with a more detailed and in depth information on industry's recommendations and commitments. Again, we welcome your input and advice for improving on these recommendations.

As you know, parents have relied on pediatric OTC cough and cold medicines and many physicians have recommended them for decades. We know pediatricians recommend them as well because in one study we know that over 50,000 pediatricians recommend them every week. Today, millions of American safety and effectively use these medicines. Just last year, there were nearly 4 billion doses sold in the United States.

These medicines are indicated and marketed to reduce

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symptoms such as nasal congestion, running nose and coughs, not to treat and cure conditions. According to national surveys, 9 out of 10 parents say these medicines help their children breathe more easily, feel more comfortable and relieve their cough.

Over the past few months, CHPA and our member companies have conducted an extensive review of the available safety data for all cough and cold ingredients. Our goal is to try to get a complete picture of what is going on and determine what actions we could take that would have the most positive impact on children and their caregivers. We also convened a panel of outside, objective experts to analyze the data, from pediatric and forensic toxicologist to critical care pediatricians and directors of poison control centers.

Their conclusions, which you'll hear today, are consistent. The vast majority of consumers are using these medicines properly and serious adverse events are very rare. Why I won't go into all of what they found, there was one overriding trend, a clear association between serious events and misuse resulting in overdose. This association we're seeing most often in children less

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than 2 years of age.

We, the industry, have always taken aggressive action to ensure the safety and safe use of our medicines, from child resistant and tamper-evident packaging to working with FDA on the development of the over-the-counter facts label. We intend to do no less

with this issue.

Before we review our specific findings and recommendations, I want to reemphasize that various data show that these pediatric cough and cold medicines are safe and effective when used as directed. Our recommendations include an aggressive risk minimization plan with label changes and a robust educational program to reduce misuse and improve safe use as well as our commitment to new research to confirm the efficacy of these medicines.

Because we found that most of the deaths, however rare, were in children under 2, because there is no FDA approved dosing in children under 2, and because our research shows that consumers were confused by the instruction to ask a doctor before dosing a child under 2, we do not believe that parents should be using these

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medicines in children under 2 and are recommending changing these labels to read "do not use in children under the age of 2" on all children's cough and cold medicines.

In addition, companies have voluntarily withdrawn all infant cough and cold medicines intended for infants less than two and have removed all images and references to infants from the packaging. In children age 2 to 12, data again show these medicines are safe and efficacious of therapeutic doses. However, because our reviews have shown an association with some overdose from misuse, and largely accidental ingestion in these ages, we are taking aggressive action to protect children.

We have also learned that there is a misconception amongst parents, caregivers and even some physicians that antihistamines, such as diphenhydramine can be used to sedate children. This is an area where we strongly believe we can have a positive impact. In addition to aggressive education, we recommend labels on monograph antihistamines should read, "do not use this product to sedate your child."

In addition to these label changes, industry will be

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launching a national education campaign. The program is designed to address the root causes of misuse and to ensure that consumers and healthcare providers understand

and follow the label. I will discuss later our target metrics and in-market monitoring to measure success of our programs. We plan to work with experts in the field to conduct sophisticated surveillance that will measure the effectiveness of our programs and our messaging. We will also work with existing systems to track outcomes and to provide interventions where appropriate.

We are also recommending new research. We will conduct a safety study to further probe the misuse and overdose issue and ensure that we understand consumer behavior in this regard.

While efficacy is well proven in adults and pediatric efficacy have been considered sufficient for years, science is evolving. Today, we have a pediatric research infrastructure in place. We also have a greater understanding of how to obtain pK data in children under the ages of 2 between the ages of 2 and 12 years of age, compared to the past, where such research was considered unethical and impractical. Thus, we are committed to

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conducting pK studies where appropriate and exploring strategies to bridge to efficacy, including end point validation with the FDA and other experts. We'll later provide more detail around many of these initiatives.

Before I introduce the rest of the speakers, I'd like to clarify a point from the previous discussion. There is evidence of efficacy for these ingredients in cough and cold. Most of it, I must admit, is in adults and we will be happy to show you this evidence either in the presentations or in our Q&A.

With these commitments in mind, here's our agenda for the rest of the presentation. Dr. Phil Walson, pediatrician at Cincinnati Children's Hospital will talk about the issues surrounding pediatric efficacy research and his recommendations for the industry moving forward. Dr. Kathy Gelotte of McNeil Consumer Healthcare will discuss the existing and potential pharmacokinetics data.

Then Dr. Ed Kuffner from McNeil and Dr. Richard Dart, a clinical toxicologist and director of the Rocky Mountain Poison and Drug Center will present the safety data and analysis. I'll then return to present and detail our proposals for risk minimization, measure to monitor

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its success and generation of new data.

I'd like to ask that you hold questions until all the presenters have finished. And without further delay, I introduce Dr. Walson.

DR. WALSON: Good morning. I'm speaking to you today as a pediatrician, clinical pharmacologist and medical toxicologist who has treated thousands of children, who's run two certified poison control centers and conducted more than 200 clinical trials, mostly in children, including multiple studies of over-the-counter antipyretics analgesics in children who had cough and cold.

Recently, industry asked me to review the existing efficacy data on OTC pediatric cough and cold medications as well as the issues associated with conducting pediatric studies. As many of you know excuse me. Many of you know how difficult it can be to conduct trials in children. It is particularly challenging in cough and cold. However, recent advances have created an environment more conducive to conducting well-designed pediatric trials. While it's still difficult, we are building an infrastructure as well as Dr. Suydam has just

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mentioned in gaining the knowledge and experience necessary to do appropriate pediatric studies, but only once we develop sensitive, validated, age-specific end points. This meeting gives us all an opportunity to take a fresh look at what's been done, what's needed and what can be done in the future.

In this presentation I'll briefly summarize the relatively large number of adult efficacy studies that have been conducted with cough and cold medicines and compare these with the relative few pediatric studies that have been done. I want to make the following three points. First and foremost, we know from adult studies that these medicines work. But they can only be shown to work if the methodology is appropriate and the sample size is sufficient.

Second, while there have been design problems with all available pediatric studies, the fact is that some pediatric studies have shown efficacy, even in children as young as 6 months of age. And third, we've already begun to conduct some of the studies we need, such as the pK

studies needed to design the dosing regimes that mimic adult drug exposure. And we're beginning to develop and

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validate the age-specific end points we need for clinical efficacy studies in pediatric populations.

But before we review the pediatric data, let's look at the adult trials. There are a number of well-designed, randomized, double blind, placebo-controlled trials where efficacy was demonstrated across a range of cough/cold active ingredients, both alone and in combination. Importantly, most of these trials had more than a hundred subject per treatment arm. And as was shown in a paper by Dr. D'Augustino in a meta analysis of antihistamine studies in adults, in order to show an effect one may need as many as 140 subject per treatment arm.

It's important to keep this in mind as we look at the pediatric studies. There are relatively few placebo-controlled pediatric studies reported in the literature. But in fact, some claimed efficacy. Some did not, and one was equivocal. All had design problems, as I said, by contemporary standards as noted in the FDA briefing document. For example, the sample size was small compared to the adult studies, 20 or 30 children versus more than a hundred adults per treatment harm.

Now, I will compare two positive adult studies, one

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in cold, one in cough to two pediatric studies where substantial improvement was seen in all of the pediatric groups, but the differences between placebo and active drug were not statistically significant. The purpose of this comparison is to illustrate the challenging in doing valid pediatric cough/cold studies, not to criticize any of the authors.

(Slide)

DR. WALSON: This graph illustrates one of the findings of the Eccles 2005 adult study where the differences between active drug and placebo were statistically significant. There were 238 subjects in this study and the primary end point was an objective measure, nasal airway resistance. The X-axis on this figure represents time after dosing. The Y-axis represents the change in nasal airway resistance.

These adult subjects were recruited within three

days of the onset of their illness from home. Active drug showed a statistically significant decrease in nasal airway resistance whereas placebo showed a slight increase or no change at three and four hours, a pharmacologically relevant time after dosing.

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Now, let's compare this to a pediatric study where both groups showed improvement for runny nose and nasal congestion, but the differences between active drug and placebo were not statistically significant. In the pediatric study, the number of subjects was small, 59. And a third-party assessment of symptoms, by a parent, was used as a subjective end point.

There were also differences in inclusion/exclusion criteria. In the adult subjects, as I said, subjects were enrolled within three days of onset, where in contrast, the pediatric study included subjects up to seven days after onset and only patients who went to a doctor for their symptoms were recruited. There were many other differences between the studies that may be responsible for the different results. One, for example, in the adults study, subjects were hospitalized, while in the pediatric study subjects were ambulatory.

Now, this is an example of a patient using the equivalent that was used to measure nasal airway resistance in the Eccles study of adults from the previous slide. It's clear why this objective, validated outcome measure was not used in the pediatric studies. Even if

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you downsized the equipment, try to imagine it being put on a child, especially one less than 2 years of age.

(Slide)

DR. WALSON: Now, here's another example or another comparison of another adult and pediatric study, this time in acute cough. The adult study showed statistically significant differences between placebo and dexromethorphan. This study also used an objective end point, a computerized cough measurement system; CCMS abbreviated, and measured response for up to three hours post-dose.

The pediatric study compared the same medicine with placebo, but here the end point was also third-party report of subjective symptoms. In addition, cough

frequency was evaluated in the morning after a single dose of medication. Now, there was substantial improvement seen with both placebo and drug compared to the night without treatment. But the study failed to detect any statistically significant differences between the two. These two studies emphasize the need for validated, age-specific end points. The difficulty in designing pediatric studies and the issues with relying on

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third-party reported data.

So to summarize, some of the lessons we've learned from these and other comparisons, first, in pediatric OTC cough and cold studies outcomes depend, not only on the right amount of medicine, but also on the recommended frequency and duration of dosing. Second, if sample size is inadequate, you can fail to demonstrate an effect, even when one is present, statistically significant and clinically relevant. Third, end points and methods that work in adults can't necessarily be used in pediatric studies because we don't want to subject children to inadequately designed studies.

So from these and other lessons, we can begin to design a contemporary efficacy program that addresses all of the problems with previous studies. This program may exclude extrapolation from adult data, a scientifically valid method, which you will hear more about from Dr. Gelotte.

I'd like to emphasize that it is important to treat the symptoms of cough and cold in children. For example, we know that cough, if left untreated, can lead to vomiting and dehydration, especially in children. Also,

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persistent coughing can spread colds. Treating cough and cold symptoms decreases unnecessary healthcare costs and decreases the use of less well-studied, risky, ineffective therapies. Also, this follows a rule of medicine. If you can't treat the cause of a condition, you should treat the symptoms to make the patient feel better, whether that patient is an adult or a child.

In summary, the data show cough and cold medicines have been well studied and proven effective in adults, both alone and in combinations. There is evidence of efficacy of these medicines in children, although clearly

more data are needed. All of the pediatric studies to date suffer from methodologic problems, which can explain the lack of consistent proof of efficacy. In addition, there is evidence that suggests that the type and sequence of cold symptoms are similar in children over 2 years of age to adults and this and other data support the validity of extrapolating adult efficacy to children.

Some pK studies have already been done. Others are being planned and we are beginning to validate age-specific, sensitive end points for pediatric efficacy studies. We are now at a point where we can bring

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clinical, scientific, government and industry expertise together in a workshop and come to consensus on appropriate methods and end points for efficacy studies in this population.

Now, I'd like to turn the podium over to Dr. Gelotte.

DR. GELOTTE: Good morning everyone. I'm Kathy Gelotte, Senior Director of Clinical Pharmacology at McNeil Consumer Healthcare. I'm here today to show how pharmacokinetics is a practical tool to help identify appropriate does in children. Such data should guide our decisions on whether and how to change recommended doses in the cough/cold medicines. These dosing decisions should be based on the relationship to more extensive adult data and on the growing accumulation of pharmacokinetic and metabolism data in children.

Before addressing dose extrapolation with pharmacokinetics, I'd like to briefly review the basis for the current dose recommendations in the monograph. In the past, the adult dose has provided the reference point for adjusting doses in children. These adjustments were based on body weight or surface area rules, resulting in doses

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that are of proportion of the usual adult dose.

In the 1976 Federal Register Notice of Findings by FDA's review panel on cough and cold drugs, the panel commented that dosing based on age may be the least reliable method because of the large variation in weights at a specific age. However, for OTC products they concluded dose recommendations based on age are the most reasonable and easily understood by the consumer. They

also recognized that effective doses for children and adults depend on several factors, including individual sensitivity, age, weight, drug metabolism and pathological conditions.

As you will hear later in the presentation, the scientific tools we have today can begin to address some of these questions.

(Slide)

DR. GELOTTE: This table highlights the basis for recommended doses by age and weight. It shows that cough/cold doses generally follow the pattern provided by Clark's weight rule for average weight across each pediatric age group.

Let's walk through one example to calculate the dose

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for children ages 6 to less than 12. The average weight from growth charts is about 71.5 pounds. When divided by 150, the weight of an adult, the fraction is about one half the adult dose for these children. Although doses were derived from the average weight in each group, dosing instructions on the label for cough/cold products are listed only by age. You can see an example here for children's Sudafed liquid showing the chart for dose by age.

One point to keep in mind is that dosing instructions on labels of OTC analgesics are different. They include weight divisions, along with age breaks on the chart, which provide further guidance to parents when selecting doses for children. From where we were in the last '70s, pediatric clinical research has evolved significantly. Pharmacokinetic studies in children are more common, thus, providing the additional data to select doses.

There have been opportunities to obtain pediatric pharmacokinetic data for a couple of OTC drugs. These occurred when combining a monograph drug with one regulated by a new drug application, which needed

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pre-approval by FDA. The clinical development programs included pediatric pharmacokinetic studies. In addition, approval was based on open label safety studies in children and on the extrapolation of efficacy from adults.

I'd like to point out that dose selection for the

new products was not straightforward because the dosing charts for ibuprofen and pseudophedrine, for example, have different numbers of age/weight divisions. Although, analgesics have more divisions, doses consistent with the monograph for pseudophedrine and chlorpheniramine were eventually selected. We'll see later how pharmacokinetic data from these applications can guide decisions on appropriate doses.

Next, I'd like to discuss the use of pharmacokinetics as a tool in pediatric drug development. A key point is that adult and pediatric pharmacokinetics do not need to be the same to extrapolate doses that would correspond to effective adult doses. We often find that elimination half life is shorter and that the weight-adjusted clearance is higher in children. However, there are exceptions. For dose extrapolation the pharmacokinetic parameters that describe drug exposure are

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considered. These are the maximum concentration and area under the curve.

The underlying assumption for dose extrapolation without subsequent efficacy trials is that the likelihood of the disease progression and the response to the pharmacological intervention are substantially similar between children and adults.

Before reviewing the cross-study comparison of drug exposure and doses, I'd like to comment on age differences and half life reported for some OTC drugs. Data for two Rx antihistamines are added to further illustrate the trend.

(Slide)

DR. GELOTTE: This chart shows that half lives in adults are generally longer than those measured in children. Although data are limited for children ages 2 to less than 6, drug disposition, including half life and clearance is considered comparable to children ages 6 to less than 12. The reason for this finding is that most developmental changes in renal and hepatic function are complete by about 1 year of age.

So what does a shorter half life tell us about the

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drug? It means that there will be less drug accumulation in children compared with adults when multiple doses are

given over the day. Another important point is that half life also guides selection of the frequency of dosing. In other words, drugs with short half lives are often dosed more frequently than drugs with long half lives.

Now, I'd like to turn our attention to the use of pharamcokinetic data to determine pediatric doses. The cross-study comparison of pseudophedrine pharmacokinetic data presented in the next series of slides differs somewhat from the review outlined in FDA's briefing book to the committee. For example, includes data from several studies in adults and children, which are listed here. In addition, the comparison includes drug exposure for multiple-dose regimes with doses administered every four to six hours. Although different datasets were considered in a cross-study comparison between adults and children, our conclusions are generally consistent with those of the FDA.

With these pharmacokinetic data, we can construct a graph of the relationship between dose and maximum drug concentrations for each age group. Beginning with adult

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date, the maximum concentrations that are obtained for a series of doses are plotted on the Y-axis. A linear relationship is apparent. When data for doses and maximum concentration in children from 6 to less than 12 years are overlaid on this graph, the linear relationship has a different slope.

To compare peak drug concentrations by extrapolation, a line is drawn up from the 60-milligram dose until it intersects the adult line and then it is drawn horizontally until it crosses over the children's line. This shows that peak concentrations of a 30-milligram dose, which is the OTC dose in children, are comparable with peak concentrations in adults.

(Slide)

DR. GELOTTE: Next, we overlay data for the youngest children from 2 to less than 6 years, starting from the 60 milligram dose in adults and crossing over the dotted line intersects approximately at the 15 milligram dose. Overall, this figure shows that peak concentrations after single pseudophedrine doses in children are comparable to mean peak concentrations after single 60 milligrams of pseudophedrine in adults.

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The same graph can be constructed between single doses and total exposure, which is the area under the curve. Again, for adults the relationship between AUC and dose is linear within this range of doses. Next, we overlay the data for children 6 to less than 12 years, draw a line up from the 60-milligram adult dose and cross over to the children's line.

(Slide)

DR. GELOTTE: Here we see that the intersection occurs at an extrapolated dose that is somewhat higher than 30 milligrams. However, there are three placebo-controlled clinical trials in adults that show the 30-milligram dose of pseudoophedrine is also effective, either when given alone or in combination with ibuprofen and chlorpheniramine.

So within this region, the children's AUC falls between two effective adult doses. For children 2 to less than 6 and the 15-milligram dose, the AUCs are lower than adults given a 60-milligram dose, but they are also within the region of both effective doses.

These data show that pharmacokinetic extrapolation is practical and informative, and that there are maybe

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opportunities to refine the pediatric doses. Citing lower area under the curve exposure data in children after single pseudophedrine dose, FDA has suggested that higher OTC doses may be considered. We agree with FDA that the current doses could be refined based on pharmacokinetic data. But we request that additional information be considered in future evaluations.

Potential approaches to refined doses include increasing the number of age/weight divisions and selecting the optimal frequency between multiple doses. These suggestions are addressed in the next two slides. However, when new pediatric pharmacokinetic data for other OTC drugs become available, further refinements, such as increasing the dose may be needed, depending on the extent of the pharmacokinetic differences.

(Slide)

DR. GELOTTE: As discussed previously, cough/cold drugs have fewer age divisions for dosing on the label. This provides the first opportunity to refine doses within

the framework of the monograph. With fewer divisions, there is a greater spread in the doses per body weight across a range of ages. The pattern is illustrated here

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for pseudophedrine. To construct the relationship between weight-adjusted dose and age, the recommended dose for the whole age group is divided by the average weight in kilograms for children at each year of age.

What this graph illustrates for the 15-milligram dose in the 2 to less than 6 year age group is that the maximum dose per kilogram is given to children who are 2-years old, whereas the minimum dose per kilogram is given to children who are 5-years old. This graph also shows an even greater spread in dose per kilogram for children ages 6 to less than 12. Yet this doesn't make sense that older children in each age division are getting less medicine per weight than the younger children.

If we consider increasing the number of age divisions for cough/cold drugs, we can smooth out the dosing pattern. In addition, this change would align with current OTC analgesic dosing regimes. The blue line depicting the current monograph doses is overlaid in this figure to highlight the increase in doses for the older children in each age group -- ages 4 and 5 and ages 8, 9, 10 and 11. With more age divisions, older children within each age group would receive higher milligram per kilo

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doses, resulting in greater drug exposure or AUC.

Another potential approach to refining recommended doses based on pharmacokinetic information is to optimize the dosing frequency. Because several doses of medicines are administered to children during the illness, the dosing frequency is important to consider as part of the dosing regime.

(Slide)

DR. GELOTTE: This figure shows that concentrations for multiple doses of 60 milligrams pseudophedrine in adults are dosed every six hours. The profile for 30 milligrams dosed every six hours in children is overlaid for comparison. As discussed previously, a shorter half life in children leads to less drug accumulation when compared with adults and when they're dosed at the same dosing frequency. This is reflected by lower plasma

concentrations at later times.

However, pseudophedrine maybe dosed every four to six hours according to the monograph. Using the pharmacokinetic data in children, we are able to simulate concentrations in the blood for the four-hour dosing frequency. When the simulated profile is added, it

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reveals that drug exposure in children encompasses that for the 60-milligram multiple doses in adults. This analysis suggest that the optimal dosing frequency for pseudophedrine in children maybe 30 milligrams every four hours.

As shown with the cross-study comparison of pseudophedrine pharmacokinetic data in children and adults, extrapolation is a practical approach to assess pediatric doses and also the frequency of dosing. This comparison reveals more than one approach to refine current monograph doses. Yet, it's important to keep in mind that every drug is unique with potential differences in disposition between children and adults. The extent of these differences may affect the selection of pediatric doses.

Toward this end, CHPA member companies are committed to obtain pharmacokinetic data for several ingredients in children ages 2 to less than 12 years. These data can guide future decisions on whether and how to change recommended doses for cough/cold drugs in the monograph.

Thank you for your attention, and I'd like to introduce Dr. Kuffner to speak on the review of safety

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data.

DR. KUFFNER: Good morning. I'm Ed Kuffner. I'm a medical toxicologist and senior director of medical affairs at McNeil Consumer Healthcare.

Today I'm presenting safety data. My safety presentation will focus on two areas. I'll present data from published and unpublished clinical trials in which recommended doses of cough and cold medicine were administered to children and adverse events were recorded. Most of my presentation will focus on an analysis of data from McNeil's post-marketing safety database of over-the-counter pediatric cough and cold medicines.

Cough and cold medicines have been studied

prospectively in children less than 12 years of age. We identified 54 published and unpublished clinical trials, including children less than 18 years of age. The number of children exposed to recommended doses of the various cough and cold medicines is listed. The number of children less than 12 years of age exposed to a recommended dose is also listed.

Most of the children in these trials were in the 6 to less than 12-year age group, but all of these medicines

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have been studied in children less than 6 years of age. Very few children less than 2 years of age were studies. Overall, the adverse events that were reported in these clinical trials were self-limited and recommended doses were well tolerated.

The specific adverse events were as expected based upon the mechanism of action and the clinical pharmacology of each ingredient. I can answer additional questions regarding specific trials and specific adverse events during the Question & Answer period.

Now, I'm going to present an analysis of data from McNeil's post-marketing safety database. It's important to remember that most of the cough and cold medicines within this dataset are regulated by the monograph process. In contrast to NDA products, monitoring and reporting of adverse events is voluntary. Over the years, the coding of adverse events has been handled differently because definitions used to categorize and code reports have varied over time there his herengenity of the data.

In order to use this dataset in a more meaningful way to guide public health decisions, it was necessary to perform a case-level review of the reports that were coded

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as serious and recategorized them using standard definitions.

Before we review the data together, let me give you an example that will put these reports and the need for recategorization into perspective. For example, a parent reports that their 3-year-old child was found with an open bottle of a pediatric cough and cold medicine and a large amount was missing. Because there may have been an overdose, the case is initially coded as serious. When you read the case details, the child went to an emergency

department, was observed for six hours and did not develop any symptoms. They were discharged from the emergency department.

This is a typical scenario. As a toxicologist, this is certainly my experience with many of the children that I referred for healthcare evaluation and many of the children that I cared for in the emergency department. Despite the fact that this child did not develop any clinical symptoms, the report is coded and maintained within the post-marketing database as a serious event. This underscores the need to reanalyze all of the cases coded as serious.

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Let's go through the analysis together. The dataset contains reports representing about 38 percent of all pediatric cough and cold medicines distributed in the United States. This dataset covers 27 years and contains reports dating back to 1980. To put some context around the exposure for this data, for this specific dataset, there are between 500 and 600 million doses of pediatric over-the-counter cough and cold medicines distributed each year.

Each week a pediatric over-the-counter cough and cold medicine is used by approximately 12 percent of children less than 6 years of age and about 8.5 percent of children between 6 to less than 12 years of age. The numbers that I would particularly like you to focus on are those for the distribution of pediatric cough and cold medicine use.

Eighteen percent of pediatric cough and cold medicines are used by children less than 2 years of age. 39 percent of all pediatric cough and cold medicines are used by children 2 to less than 6 years of age and 43 percent of all pediatric cough and cold medicines are used by children 6 to less than 12 years of age. In this

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presentation I'm going to compare the percentage of all reports and the report coded as serious in these different age groups to the percentage of overall use of pediatric cough and cold medicines in these different age groups. So remember 18 percent, 39 percent and 43 percent.

(Slide)

DR. KUFFNER: This slide represents the dataset

containing all reports in children less than 12 years of age with a cough and cold medicine. Across the top row are the ages, less than 2 years, 2 to less than 6 years and 6 to less than 12 years as well as age unknown. You see the absolute number of reports in the first row and the percentage of total reports below. At the bottom of the slide is the distribution of over-the-counter pediatric cough and cold medicine use across different age groups 18 percent, 39 percent and 43 percent.

When considering the distribution of cough and cold medicine in use, reports in children less than 2 years within the dataset appear to be significantly over represented. While 18 percent of the use of cough and cold medicines occurs in children less than 2 years of age, 33 percent of the reports occur in this age group.

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In comparison, 39 percent of the use of cough and cold medicines occurs in children 2 to less than 6 years of age and 49 percent of the reports occur in this age group. Further analysis of the data revealed some potential reasons why there appears to be over representation of reports for children in these age groups.

(Slide)

DR. KUFFNER: The data shown here summarizes all the reports in children less than 12 years of age in the dataset. You see the number of cases coded as non-serious, serious or fatal. Of all the reports within the data set, 96.8 percent were coded as non-serious. There were 74 total fatal reports. All of these fatal reports were submitted to and reviewed by the expert panel. I'm not going to discuss the fatal reports further because all of these were included in the expert panel analysis that Dr. Dart will be presenting.

There were 562 reports that were coded as serious. These are the reports we reviewed, recategorized and analyzed further. Remember, although these reports were coded, as serious, serious clinical events based upon the regulatory definition of a serious, adverse event

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oftentimes were not reported.

Across the top row are the age groups. Within each age range, you see all reports, the reports coded as serious and the percent of reports coded as serious.

Reports coded as serious represent a relatively small percentage across all age groups. The analysis we're going to go through together is the result of a case-level review of individual reports coded as serious. Ultimately, the reason for this detailed review was an attempt to understand these reports in the context of a public health issue. Remember, not all reports coded as serious had clinical effects.

By performing a case-level review of all reports coded as serious, we were able to classify them and classify the reported reason for exposure, the reported dose ingested and the clinical effects, if any, which were reported following exposure. In this way we were able to determine if a report coded as serious truly had clinical affects; and if so, the seriousness of those clinical effects.

(Slide)

DR. KUFFNER: This slide gives you a roadmap for the

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analysis we are going to go through together. The reason for exposure was classified into one of three categories accidental ingestion is a child getting into a cough and cold medicine on their own when the medicine was not appropriately kept out of their reach; use for labeled indication is the presumed use of a cough and cold medicine for the treatment of cough and cold symptoms. If another reason for exposure was not specifically mentioned, the report was classified here. Other includes two categories malicious intent and use for unlabeled indication.

When it was reported that there was suspected or confirmed abuse, reports were coded as malicious. When a cough and cold medicine was administered for a non-cough and cold indication, such as sedation, reports were classified as use for unlabeled indication. When the reported dose could be determined, it was classified as either a therapeutic dose or an overdose. Each report was reviewed to determine what clinical effects, if any, were reported. Clinical effects were classified as asymptomatic or no adverse event reported, mild effects, moderate to severe effects, unable to assess or unrelated

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to the cough and cold medicine.

Before we begin this review, it's important for you to understand that not all cases coded as serious developed clinical effects. In fact, of the 562 reports coded as serious, 194, representing 34 percent, had no clinical effect reported; 119, representing 19.6 percent had only a mild clinical effect reported. There were 218 reports over 27 years in which a moderate to severe clinical effect was reported. It is extremely important that you understand the distinction between a report coded as serious and a report in which a moderate to severe clinical effect was actually reported.

Now, we're going to systematically go through these reports. We're going to start with accidental ingestion. Fifty-four percent of the reports coded as serious were cases where a child got into either an adult or a pediatric cough and cold medicine on their own. In these cases, the medicine was not appropriately kept out of the reach of a child.

Let's try to understand the accidental ingestions. Across the top row are the age groups. Within each age range you see all reports of accidental ingestion, the

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reports coded as serious, all reports of accidental ingestion and the percent of reports coded as serious. Accidental ingestion is more common in children 2 to less than 6 years of age and is the leading cause for reports coded as serious within that age group.

In children 2 to less than 6 years of age, 70 percent of all the reports coded as serious were unrelated to the use of a cough and cold medicine for the treatment of cough and cold symptoms. In children less than 2 years of age, a full 41 percent of all the reports coded as serious were also unrelated to the therapeutic use of a cough and cold medicine. We identified 301 accidental ingestion reports.

Now, let's try to understand the clinical effects, if any, that were reported following these accidental ingestions. Since accidental ingestion is most common in children 2 to less than 6 years of age, and since it's the leading cause of reports coded as serious in this age group, we'll focus on the 2 to less than 6-year age group.

Across the top row are the age groups. Within each age group, you see the clinical effects that were documented

in the report.

Accidental ingestion of cough and cold medicines are usually not associated with clinical effects. In fact, 56 percent of the accidental ingestions that were coded as serious did not result in any clinical effects being reported. Again, it's important for you to understand that although these reports were coded as serious and maintained within the post-marketing database with that code, no adverse clinical effects were reported; 26 percent resulted in a mild clinical effect and only 18 percent resulted in a moderate to severe clinical effect.

This data is consistent with poison center data that will be discussed by Dr. Dart and is similar for exposure to other over-the-counter medicines as well as prescription medicines. Failure to keep medicines out of the reach of children results in preventable, accidental ingestions. All of the moderate to severe clinical effects was self-limiting and when the reported dose could be determined all of the reports of accidental ingestion in which a moderate to severe clinical effect was reported were reported overdose.

We're now going to focus on the use for labeled indication. We identified 239 reports where it was presumed that the cough and cold medicine was administered to a child for treating cough and cold symptoms. When cough and cold medicines are used for the labeled indication, considering the distribution of product use, there is an over representation of reports coded as serious in children less than 2 years of age. While 18 percent of the use of cough and cold medicines occurs in children less than 2 years of age, 29 percent of the reports coded as serious with use for labeled indication occur in this age group.

In comparison, 39 percent of the use of cough and cold medicines occur in children 2 to less than 6 years of age, and 41 percent of the reports coded as serious occur in this age group.

Now, let's try to understand the dose that was administered to a child when a cough and cold medicine was used for a labeled indication. In 138 reports, it was reported that a therapeutic dose was administered. In 53

of the reports, it appeared, based on the data, than an overdose was administered. In 48 of the reports, we were unable to determine if a therapeutic dose was administered or if there was an overdose.

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Now, we'll review reports where it was reported that a therapeutic dose was given. Across the top row are the age groups; the reported dose ingested is listed in the column on the left. Doses are classified as either therapeutic dose or other. Within therapeutic dose we had three categories, dosing as per the OTC label, monograph professional dosing, or extrapolated dose. In the other category, we have overdose or reports where the dose was unknown.

For over-the-counter cough and cold medicines there is no dose on the label for children under 2 years of age. For cough and cold medicines that contain an antihistamine, there is no dose on the label for children less than 6 years of age. Therefore, by definition, these children could not have received a labeled therapeutic dose. The medical literature and other sources provide extrapolated therapeutic doses for cough and cold medicines for children less than 2 years of age. Of the 69 doses administered to children less 2 years of age, 34 were determined to be an extrapolated therapeutic dose.

In no report was it documented how caregivers may

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have arrived at this extrapolated dose. It is unknown whether the label instructions were followed and a doctor was consulted or whether the dose was determined by other means.

For children less than 6 years of age, there is a specific dose on the OTC label for cough and cold medicines, which do not contain antihistamine. In 17 of the 97 reports, use of a labeled therapeutic dose was documented. When a cough and cold medicine contained an antihistamine, a therapeutic dose for children 2 than less than 6 years of age was based upon professional dosing as outlined in the monograph. In 35 reports, the dose administered was reported to be a therapeutic dose based upon monograph professional dosing.

Similar to children under 2 years of age, it is

unknown whether the label instructions were followed and a doctor was consulted or whether the dose was determined by other means.

In all of the 18 reports of overdose in children less than 2 years of age, there was no specific dose on the over-the-counter label. In 24 of the 27 reports of overdose in children 2 to less than 6 years of age, there

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also was no specific dose on the over-the-counter label.

Now, we're going to discuss those reports were a cough and cold medicine was used for a labeled indication and the reported dose that was ingested was an overdose. Let's try to understand the root causes of overdose when cough and cold medicines are used for labeled indications.

Some reasons for overdose include administering an adult cough and cold medicine to a child, administering multiple products containing the same active ingredients at the same time, and administering medicines too frequently.

By far, the most common root cause for overdose in children less than 2 years of age and in children 2 to less than 6 years of age is incorrect dosing. Although the reason for incorrect dosing could not be determined from the case-level review, there are far fewer reports of incorrect dosing in children 6 to less than 12 years of age when a specific dose for children of this age is listed on the over-the-counter label.

For all of the 13 reports in children less than 2 years of age, and for 20 of the 24 reports in children 2 to less than 6 years of age where an incorrect dose resulted in an overdose, there was no specific dose on the

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over-the-counter label for children in these age ranges.

Using data from the case-level review and product distribution data, reporting rates were calculated. Across the top row are the age groups, the reporting rate for a report coded as serious regardless of whether an actual adverse clinical effect was reported are listed for each age range and each reported dose ingested per 1 million consumption units.

Considering exposure data, the reports coded as serious with the use of a cough and cold medicine for a labeled indication are very rare. In this dataset, for children less than 2 years of age, use of an

over-the-counter pediatric cough and cold medicine for a labeled indication was associated with a report coded as serious at a rate of 0.073 times per 1 million doses distributed. The rates for children less than 2 years of age for every dose category are higher than the rates in all other age groups.

Also shown are the reporting rates for reports coded as serious per 1 million doses distributed when the specific dose was and was not on the OTC label. Whenever the dose was not on the OTC label, the reporting rate was

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higher than when the dose was on the OTC label. The highest reporting rate when the dose wasn't on the OTC label was for children less than 2 years of age.

As an industry, we talk all reports of adverse events associated with the use of pediatric over-the-counter cough and cold medicines seriously. As a father and as a clinician, I know that every child is precious. Overall, adverse events that were reported in clinical trials were self-limited and recommended doses of over-the-counter cough and cold medicines were well tolerated.

Post-marketing databases have their limitations. That being said, there is a long history of use of over-the-counter cough and cold medicines in children and this dataset dates back 27 years. The post-marketing database supports findings from the clinical trial database that when used as directed and administered at therapeutic doses, over-the-counter cough and cold medicines are well tolerated.

When the post-marketing databases reviewed in the context of use, one can conclude that reports coded as serious from accidental ingestion, from therapeutic use,

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and from overdose are very rare. In children 2 to less than 6 years of age, accidental ingestions account for the vast majority of serious adverse events. The development of moderate to severe clinical effects following accidental ingestion is unusual. Therapeutic doses in children 2 to less than 12 years of age appear to be well tolerated.

There is an over representation of reports coded as serious in children less than 2 years of age. While most

caregivers administer cough and cold medicines appropriately, rare instances of misuse, leading to overdose, occur, especially in children less than 2 years of age. It appears that a lack of a specific dose on the OTC label for age ranges in which over-the-counter cough and cold medicines may be used maybe associated with incorrect dosing and overdose, and used as directed, over-the-counter cough and cold medicines are well tolerated. Thank you.

I'd like to introduce Dr. Dart.

DR. DART: Good morning. My name is Rick Dart. I'm a medical toxicologist for about 20 years and director of the Rocky Mountain Poison and Drug Center for the past 15

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years. I'm also the parent of three girls, wonderful girls 6, 9 and 11 so I'm still using these medications actually, although my kids still think that I treat them like they're 2-years old.

What I'm going to do today is try to address the poison center date on safety. I'm going to talk about the data and the fatalities associated with the OTC cough and cold medicines. I'll start by describing the National Poison Center data and the criteria that we use to guide these patients, manage these patients when they call the poison center. Finally, I'll present the conclusions of a consensus panel that examined all the fatalities that we could find.

Now U.S. poison centers are a nationwide network that provides advice to the public and to healthcare professionals. There are 61 poison centers covering every state. Every call is managed by a trained professional, mostly pharmacists and nurse. Our callers range from mothers worried about their child to healthcare professionals managing critically ill patients. All poison centers document their calls using a nationally standard system. This system allows us to use standard

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definitions and to collect data consistently.

The large amount of data from our system is a valuable tool for assessing drug safety. The main limitation of our data is that like the FDA's adverse event reporting system, the data come from spontaneous reporting. However, poison center data have the advantage

of being truly national and involving a large number of cases arising from the cough and cold products.

Poison centers receive two main types of cases exposure calls and information calls. An information call does not involve a person actually ingesting or being otherwise exposed to a substance while an exposure call is any call in which the patient actually took the drug or chemical involved regardless of the dose.

In 2005, poison centers received nearly 2.5 million exposure calls that's for all substances. It's very important to understand that an exposure does not mean an overdose. It could be a therapeutic dose or an overdose. For example, a common call in kids is when one child is administered the dose meant for another child. Every case is graded for outcome no effect, minimal effect, moderate effect, major effect or death.

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With this in mind, let's look at the Maryland data. The Citizens' Petition is a good example of how poison center data can be misinterpreted. The petition to FDA reported that about 900 young children overdoses on OTC cough and cold medicines in Maryland just in 2004. You see the Maryland data on this slide.

(Slide)

DR. DART: In 2004, there were more than 18,000 exposure calls that involved a child under the age of 6. Roughly, 1,000 involved a cough and cold medicine. Nearly all of those were judged by the poison center specialist themselves to result in no effect or minor effect. None were fatal or major in outcome.

Now, please recall the definition of exposure. It simply means that the patient actually took the drug or chemical involved. It does not mean that an overdose or that toxicity occurred. As you can see, the most severe effects reported were five exposures with moderate effects. This meant that the child was referred to the hospital, received supportive care and was released.

Before we look at more data, let's look more closely at the difference between overdose and toxicity. As I

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mentioned, most of the time, even an overdose does not cause harm. This is reflected in practice guidelines developed by poison centers and toxicologists. Every

poison center uses guidelines for their specialists to take calls.

Listed here are the six pediatric cough and cold agents that generate the most calls, along with their FDA labeled therapeutic dose. The next column shows the dose in milligrams at which a poison center would refer a patient to the emergency department. If the referral dose is divided by the therapeutic dose, we see that the dose must be 10 to 30 times the therapeutic dose for a poison center even to refer a child to the emergency department.

In the end, even referred hospital cases rarely develop effects needing treatment. At doses less than these thresholds, instead of sending the patient to the emergency department, we follow them at home by telephone. This does not mean that we would ever recommend such high doses for a child as treatment. It simply reflects the experience of poison centers with hundreds of thousands of exposures in children.

Now, let's look at the nationwide data. All poison

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centers submit their data to the American Association of Poison Control Centers. We asked the association to provide all cases of exposure involving a child under the age of 12 years at which a cough and cold ingredient was involved. These included prescription drugs as well as OTC medications and this includes all of the adverse event categories that were mentioned by Mike Shannon.

The period of study was January 1st, 2000 through June 30th, 2007. Almost 775,000 exposures were identified. When we look at the outcome of these exposures, the results are, again, very similar to the Maryland poison data. Ninety-seven percent of the exposures were judged by the poison center to be associated with no effect or a minor effect, 1 percent was associated with a moderate effect.

(Slide)

DR. DART: As you can see from the graph, an extremely small percentage of exposures were associated with a major effect or a fatality. But of course, these are important cases. So to understand these serious cases better, an independent, expert consensus panel was asked to analyze the poison center cases as well as the cases

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from several other sources.

Now, the purpose of the expert panel was to gather the fatalities from these sources and assess the relationship with the cough and cold medicine reported. The panel also categorized t he likely dose ingested and assessed the root cause of the fatality. The panel focused on cases involving the top eight medicines in the cough and cold category, which were identified by examining the National Poison Center database.

The consensus panel members included experts in pediatrics, critical care, toxicology, pharmacy and forensic medicine. The panel analyzed all fatality cases it could obtain. These included cases from the English language medical literature extending back to 1949; manufacturer adverse events extending back to 1980; the National Poison Center database extending back to 1983 as well as the FDA briefing material and the Citizen Petition.

Cases were limited to children of the age of less than 12 years and exposure to any one of the eight ingredients I mentioned. Panel members reviewed each case individually, then as a group, and came to complete

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consensus on every case. The panel used explicit definitions of causality. These included definitely related, likely related and possibly related as well as unlikely related, definitely not related and unable to determine.

All cases that were possibly, likely or definitely related were included in the analysis, even though many of the possibly related cases were more likely due to another cause. With every case from possibly to definitely related, the dose was estimated as therapeutic, super therapeutic or unable to determine. As you'll see, the results are similar to the Maryland and the National Poison Center data.

Overall, the consensus considered 227 cases over the period I described. Thirty-six of these cases were excluded because they were duplicates or involved the wrong drugs. Forty-nine cases were judged unrelated to an OTC cough and cold medicine. And in 20 cases, the panel was actually unable to determine whether the cough and cold medicine was related to the fatality or not. This

leaves 122 cases where a cough or cold ingredient was at least possibly related to the death in the judgment of the

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consensus panel.

Of those, 25 percent actually involved a prescription drug. Since this is OTC we're addressing today, we take those out and that leaves a total of 92 cases that involve nonprescription drugs. I phrase it that way because in order to capture all potential OTC-related cases, the panel included in the nonprescription category all case where the drug's prescriptive status could not be determined.

For example, if a coroner did levels, but didn't report the product and those were OTC levels that were measured, that was included.

Of the 92 cases, 79 were judged to have involved a super therapeutic dose by the panel. Thirteen were judged to have involved an undetermined dose. No cases were judged to have involved a therapeutic dose.

(Slide)

DR. DART: Here we see the age distribution of these cases. Of 92 fatalities, 74 percent involved children under the age of 2 years. The panel also discovered that many children being treated with cough and cold medicines did not actually have cough and cold symptoms. Of the 92

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OTC cases or nonprescription case, 93 explicitly addressed the presence of cough and cold symptoms. The panel found that 44 percent of those records specifically recorded that the child did not have cough and cold symptoms.

Well, if cough and cold symptoms were not the reason for administration, what was? The reason may be associated with the finding that emerged when the panel examined where the exposures occurred. Of the 52 exposures where the site was documented, 76 percent occurred in the home, must, as you would expect. In the less than 2 age group, however, 32 percent occurred at a day care center or a babysitter's home.

In some of the cases, and these involve both the cases at home and in the day care/babysitter setting, the caregiver reported that they were using the medicine as a way to quiet the child and did so on a regular basis.

Now, I want to point out that this, in general a

lot of these cases were during the day, not at night. So these are patients at a day care who then received medicine to quiet them. Importantly, all of the day care cases involved children under the age of 2 years. Education and training of these caregivers could produce a

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striking improvement.

The panel's analysis of root cause suggests several opportunities for decreasing misuse of these medicines. Recall that there were 92 cases over the past few decades that were judged at least possibly related to an OTC cough and cold ingredient. Of these, 18 involve the category of child administered, as the panel termed it. This refers to the classic scenario of a toddler exploring their environment and is a clear target for intervention.

If we look at the 68 cases that were administered by an adult, we find that 44, which is 65 percent of the cases, were judged to have either a therapeutic intent or the panel could not determine the intent. Twenty-three of the cases, that's 52 percent, involved an OTC combination product. That's very close to the market share for these medicines and 9 percent involved exposure to more than one product that contained the same ingredient, which, of course, is another target for intervention.

The panel judged that 24 of these cases were non-therapeutic intent, of which 20 were actually judge malicious intent. That term "malicious" includes cases in which the adult admitted sedating the child or

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intentionally trying to harm the child, and sadly, there were a few of those. The analysis demonstrates that the apparent misuse of these products and the potential for effective interventions exists.

National surveys show that millions of children are treated with OTC cough and cold medicines every year. The National Poison Center data and the consensus panel results both show that these medicines are safe when used at a true therapeutic dose. The independent consensus panel found that in all cases where a dose could be estimated an over dosage was involved. The panel found no case where a caregiver appeared to have accurately administered a therapeutic dose and the child died.

But the fact remains that there were fatalities

associated with the use of these products. Most of the deaths occur in infants. This is not surprising since it's much easier to make a dosing error when you're measuring tiny amounts of medicine. The important thing to remember is that all of these deaths were preventable. All of the areas present opportunities for intervention and prevention.

Data from over 25 years shows that the cough and

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cold medicines are safe, but like any medicine can produce toxicity in overdose. We can and must create a system to detect and prevent those events. Thank you. I'd like to return this to Dr. Suydam.

DR. SUYDAM: Thank you, Dr. Dart.

I'd like to spend a few moments summarizing what we've learned from our review and analysis of the available data, and share with you our proposed risk minimization plan, which we've developed in response to what we learned.

This plan is comprehensive and we are committed to ongoing measurement initiatives, which will continue to refine our plans going forward. Additionally, I will also share with you our research plans to further address efficacy in dosing on which we will work with the FDA immediately.

So here is what we know so far. Available data affirm that children's over-the-counter cough and cold medicines are safe when used as directed and that most serious adverse events are reported to be associated with the overdose and misuse of these medicines, especially, in children under 2. We also know that accidental ingestion

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appears to be a major factor in children 2 years and older. These are areas where new labeling and education can make a difference.

As for efficacy, we know it is well established in adults and we have additional work to do to confirm or refine dosage levels in children. CHPA has also conducted consumer research to answer issues raised by the FDA and to support industry efforts.

I'd like to summarize our consumer research results. Parents and other caregivers are motivated by a sincere desire to make their children feel better when suffering

from cough and cold symptoms and rely on these medicines to do so. Our research identified a specific need for consumer education on dosing, active ingredients and label directions. We will develop and distribute information for parents and other caregivers specific to these issues.

And since many caregivers rely on healthcare professionals for advice regarding over-the-counter cough and cold medicines for children, we will also target healthcare professionals with our message as well as part of our risk minimization plan. The goals and plans I will now outline are based on our analyses of all the data and

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will address what we've learned.

Let me begin with our goals. Our goals are threefold. First, we want to build awareness of correct use. Second, we want to change caregivers' attitudes about risks; and more importantly, caregivers' behaviors about the use of over-the-counter cough and cold medicines. Third, we want to significantly reduce misuse and overdose. We will accomplish these goals through an aggressive risk minimization plan, which I'll now describe.

Our risk minimization plan consists of four key ingredients, components assessing risks, identifying strategies, implementing programs and measuring effectiveness.

(Slide)

DR. SUYDAM: As shown in the diagram, it's a continuous process aimed at reducing risks. I'll talk about each of the four components in detail.

(Slide)

DR. SUYDAM: First, risk assessment, this slide shows the main issues we've identified that need to be addressed misuse resulting in overdose, particularly, in

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children under the age of 2; the use of OTC monograph antihistamines such as diphenhydramine to sedate children; accidental ingestion in children 2 and over; adult-strength medicine being given to children and multiple medications with the same active ingredients being used at the same time.

(Slide)

DR. SUYDAM: Second, identifying strategies, we've

identified a number of strategies to reduce these risks. As you see in this chart, we're recommending addressing the risks we've identified through label changes and education as well as implementing measurement tools and systems to ensure that our programs are successful.

There are two issues that we feel that can be addressed with specific label change along with education. The first is misuse resulting in overdose, particularly, in children under the age of 2. And the second is the use of OTC monograph antihistamines, such as diphenhydramine to sedate children.

Let me talk about each of these in detail. We recommend changing all pediatric over-the-counter cough and cold labels that read "ask a doctor" in regard to

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dosing children under the age of 2 to read "do not use in children less than 2." This will assist in preventing possible misuse and further encourage parent, healthcare provider interaction in addressing the symptoms of children under the age of 2.

And based on our findings that sedation was one of the biggest reasons for overdose, we recommend adding "do not use to sedate children" or similar consumer-friendly language for OTC monograph antihistamines to assist in preventing possible unintentional overdose of children. From our research, we know that parents clearly understand "do not use" on the label and report strict adherence to these directions.

Third, program implementation, in addition to label changes we will be launching a national, multi-year education program to help reduce the risk of overdose and misuse. Our multi-year, national education program will reinforce the label changes and it will educate consumers and healthcare professionals about the safe use and safekeeping of pediatric over-the-counter medicines to prevent overdose. And it will also enlist healthcare providers to help us educate parents. It will also

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encourage communication between healthcare providers and parents about safe use of pediatric OTC cough and cold medicines.

Our plan will be managed by an expert steering committee composed of members of top medical, government

and consumer organizations. It will be a multi-year, multimedia campaign with elements distributed through multiple channels, including public service announcements and paid advertising. It will run on parallel tracks targeted at consumers and healthcare providers. And importantly, we will touch consumers at tactical, decision-making points in their lives, such as in stores, on the Internet, in doctors' offices, day care centers and maternity wards. And with 4 million births each year, there will be a particular focus on new mothers.

To maximize chances for the program's success, we'll work with partners from a broad range of important organizations from the American Academy of Family Physicians to the American Pharmacists Association and to the FDA to develop these materials. We'll utilize their vast networks, periodicals, electronic media and conferences to deliver our educational materials about the

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new label on pediatric dosing and the correct use of cough and cold medicines.

Fourth, we will measure effectiveness. Critical to our program will be a variety of state-of-the-art measurement tools and systems to ensure that the program is effective in changing consumer and healthcare provider behavior. These will include consumer surveys conducted through household panels to track awareness and effectiveness of the program.

We will begin with a baseline survey to determine parent/caregiver attitude and behaviors regarding pediatric dosing with over-the-counter cough and cold medicines. We will establish three pilot markets in which we will conduct additional advertising and partner with the local poison control centers to monitor outcomes and provide direct interventions to help reduce misuse where needed. We will begin his process next month and then conduct ongoing surveys.

In addition, we plan to work with pediatric clinical experts as well as the FDA to design a pediatric clinical research program that will be relevant to today's science and in the best interest of children. This will include

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pK studies in children 2 and older on dextromethorphan, phenylephrine, guaifenesin, brompheniramine,

diphenhydramine and chlorpheniramine. We will determine where it is possible to bridge using pK data and where additional data is needed. We will also continue to monitor the safety of these medicines for the OTC uses. And we are committed to working with the FDA to conduct a post-market safety study.

Here is our proposed timeline for risk minimization, education and research plans. Within a year, we have proposed to have new packaging on all labels on store shelves. We will begin our education program immediately. Various elements will roll out through March of 2008 to continue through the life of the multi-year program.

Our healthcare education elements will roll out immediately and continue also through the life of the program. We will begin monitoring all of these activities, and as I just described pK study planning is already in progress.

So in conclusion, analyses of a number of different databases, including analysis by a panel of outside, independent experts have shown that the pediatric,

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over-the-counter cough and cold medicines are safe when used as directed. There are pediatric studies that demonstrate efficacy in children under 12, even as young as 6 months of age and the FDA has recognized these pediatric medicines as effective for years.

Adult efficacy has been demonstrated for cough and cold medicines in well-designed studies. The data indicate that because of rare adverse events, due to misuse, some parents and caregivers need better information to understand how to use these medicines appropriately.

We, as an industry, commit to launching a risk minimization program and a national education campaign to address these issues. We will work with the FDA and pediatric experts in the field to develop strategies to confirm efficacy in children 2 years and older. We are looking forward to working with you, with pediatric research experts and the FDA to develop the most effective program possible. Thank you for your time and attention. We'll be happy to take your questions.

DR. TINETTI: I want to thank you all for your careful presentations. We're actually almost at noon.

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I'm sure people have a lot of questions. So I think rather than starting it now, we have a lot of time this afternoon for questions. So I think it probably would be best to save the questions until this afternoon so we can have enough time to really devote to it. Thank you.

The Committee should convene in Room 9217 and remind you all to be back by 1:15 p.m. and again remind the Committee not to discuss any of the proceedings today. Thank you.

(Whereupon, at 11:42 a.m., a lunch recess was taken.)

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

DR. TINETTI: Welcome back, everyone. We're going to begin the afternoon session. Hopefully, you all got outside to enjoy the beautiful weather out there. We are going to we've asked the industry representatives and they're fine with us having the questions after the presentation from the FDA. So everybody can hold there questions and we'll have plenty of time to make sure everybody's questions get addressed after the presentations.

So next, we're going to move on to the FDA presentations. And the first is going to be Dr. Roy from the Office of Clinical Pharmacology.

DR. ROY: Good afternoon. My name is Phara Roy and I'm a senior clinical pharmacologist at the Office of Clinical Pharmacology at the FDA.

The topic of my presentation is clinical pharmacology perspectives of pediatric dosing of over-the-counter cough and cold medications. Here is the

outline of my presentation. First, I'm going to briefly describe the issues raised in the Citizens' Petition and understand the basis of the petition from a clinical

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pharmacology perspective; specifically, what we know about systemic exposure of OTC cough and cold drugs and the factors that influence drug exposure.

Clearance is the single most critical pharmacokinetic parameter that impacts drug exposure. Keeping that in mind, I'll discuss the antigen or in other words, the development of renal and hepatic clearance mechanisms with age. Then, we'll take a look at the systemic exposure data in children for three OTC cough and cold drugs. Following that, I'll address the high concentrations noted in postmortem reports and try understanding the contribution of postmortem drug redistribution.

Then I'm going to spend some time explaining the current practice of pediatric drug development, specifically addressing the FDA's current approach on the requirement of pediatric pK studies with a relevant example. And finally, I'll conclude with an overall summary of the discussion.

Let me briefly highlight the two critical bullet points from the Citizens Petition under discussion. It raised significant concerns about the safety and efficacy

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of cough and cold medications in children 6 years and younger, requested FDA to relabel these products to state that these products should not be used for the treatment of cough and cold in children under 6 years of age.

As you already know, these are the basis for the petition. Reports of deaths and serious adverse events in which drugs commonly found in OTC cough and cold preparations were detected at very high concentrations, mostly in infants and toddlers. The absence of specific dose and dosing interval information on the label for children under the age of 2 years constitutes a safety hazard in an age range highly vulnerable to overdose.

As for many of the drugs, in general, OTC cough and cold drugs undergo elimination from the body via a renal or metabolic clearance pathways.

Next, I'll discuss the development of functional

maturation of renal and metabolic pathways with age or in other words, the antigen of clearance pathways. Before getting to the antigen part, let's look at the clearance pathways of some of the representative OTC cough and cold drugs. There are two board clearance pathways; namely, renal and metabolic.

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Pseudophedrine, for example, is primarily cleared, unchanged via urine, while others undergo extensive metabolism mediated by a multitude of Sigmoidal P-450s, as you can see from this table.

First, let's look at the antigen of renal clearance. As in theory, renal maturation and growth impact drug exposure if the drug is primarily cleared via kidney. In a recent publication a model was developed that categorized the maturation and growth of the renal function parameters.

(Slide)

DR. ROY: On the graph on the right, model-predicted body weight normalized renal function parameter relative to adult weight value in the Y-axis was plotted against age in the X-axis. As shown here, body weight normalized glomerular filtration and active secretion begins to develop immediately after birth, reach adult value and then at some point exceeds the adult rates before it starts to decline again. So for the most part, renal maturation is complete by 2 years of life, then growth takes over.

Let's now look at the maturation of hepatic

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clearance with dextramethorphan as an example. This example is relevant for today's discussion since this is a widely used OTC antitussive agent that falls under the class of drugs under discussion.

The figure on your right illustrates the metabolic pathways of dextramethorphan. Dextramethorphan is metabolized by Sigmoidal P-450s to D6 and three and four enzymes followed by gluconate conjugation. Sigmoidal P-452 to 6 is believed to be the primary metabolic pathway for oral dextramethorphan clearance and has been implicated in the metabolism of many other OTC cough and cold medications. This enzyme is polymorfically expressed in humans where the systemic exposure in poor metabolizer

phenyl-types is about 100-fold greater than in extensive metabolizer phenyl-types consistent with the half life differences between the two populations.

Besides poor metabolizer phenyl-types, there exists a wide spectrum of subtypes within the extensive metabolizer category, such as intermediate, rapid and ultra rapid. The incidents of poor metabolizer phenyl-typical expression is about 5 to 10 percent in Caucasians and about 1 to 3 percent in Asians. Sigmoidal

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P-452GD6 genetic polymorphic expression is believed to be the primary cause for large inter-individual variability that we observe with dextramethorphan metabolism in adults.

These same phenomena would be applicable to children as well and would likely result in large inter-individual variability. That has been illustrated in the next slide.

(Slide)

DR. RAY: Attempt has been made as recently as this year by Blake and coworkers to characterize antigen of dextraphen metabolism after oral administration in the first year of life. Sigmoidal P452D6 activity is measured by the urinary dextramethorphan to dextraphen ratio. This ratio, on average, did not change from two weeks of life to one year, suggesting that the maturity of the enzyme is complete within the first two weeks of life. However, large individual variability was observed for each time point that is attributed to the Sip-2D6 polymorphism that I discussed in the previous slide.

This data will not include poor metabolizers. Still the variability is significant due probably to the inclusion of different extensive metabolizer subtypes.

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However, this data should be considered with caution due to several factors.

There's a limited utility of this ratio to detect subtle changes in dextramethorphan clearance. This ratio is more suited for dramatic changes seen with polymorphism. There is a different rate and extent of maturation of the competing metabolic pathways. So these observations made it impossible to reach a definitive conclusion on Sigmoidal 452D6 maturity during the first year of life.

The other important drug metabolism Sigmoidal 450, which catalyzes a number of cough and cold drugs, is Sigmoidal 453 and 4. As shown here, the maturation of the 3 and 4 activity with age has been investigated in vitro, utilizing all clearance of metabolism. A widely accepted drug from Sigmoidal 453 and 4-enzyme activity as illustrated by this plot Sigmoidal 453 and 4 exhibits a gradual increase in enzyme activity following birth in children. It has been shown that on average, 40 percent of the activity is attained by one year and about 75 percent activity attained by 2 years of life.

In contrast, body weight normalized metabolism

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clearance in 2- to 15-year-olds on average is greater than in adults. This phenomenon has also been shown with other three and four substrates in the literature.

So the main objective of the four or five slides that I have shown you is to give you a rough idea of the dramatic changes and uncertainties in drug clearance in very young children, due mostly to independent rate and extent of maturation of clearance pathways in addition to genetic polymorphism with specific enzymes such as Sigmoidal P-4502D6.

Apart from what I discussed already, there are other additional factors that affect the clearance, thereby exposure of drugs in children, many of which are poorly understood at present. These include, but not limited to, antigen of other drug metabolizing P-450s, antigen of the Phase 2 enzymes that might impact exposure, antigen of the drug transporters, which seem to gain importance in the last few years in a recent publication demonstrating effect of diet on the maturation of Sigmoidal P-450 1 and 2 and 3 and 4 enzymes. And last, but not least, effect of pH, the gastric pH that can impact drug absorption and urinary pH that can impact drug elimination.

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So to summarize, the development of clearance pathways: renal, renal maturation is complete by two years; metabolic, each drug-metabolizing enzyme demonstrate an independent rate and pattern of maturation. Genetic polymorphism of drug metabolizing enzymes impact drug exposure in children and these lead to large inter-individual variability in metabolic clearance in

children.

Next, I'm going to show you some available pK data for OTC cough and cold drugs. Before doing that, I will briefly reiterate the current pediatric dose recommendation for OTC cough and cold drugs. Decongestion, expectorant and antitussive are dosed down to 2 years, while antihistamines are dosed down to 6 years.

Children dosing is a fraction of adult dosing, half for 6 to 11-year-old and one-fourth from 2 to 5. These approximately mimics the dosing based on average body weight for a particular age range, realizing, however, that that a 2-year old can be very different from a 5-year old with respect to body weight. Professional labeling is available below the age of 6 for antihistamines. The

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label recommendation for children below 2 is consult a doctor. I would like to say that many of the assumptions that lead to monograph dosing are under discussion today.

Now, I'll present available pK data on three of the OTC drugs in the next few slides.

(Slide)

DR. ROY: One of the OTC decongestants we have for pK data down to the age of 2 years is pseudophedrine as shown in the table. Following monograph suggested dosing; the means systemic exposure in children as evidenced by peak plasma concentration and 80 under the curve is numerically lower than in adults, although this is a cross-study comparison. No pharmacokinetic data is available for children less than 2 years of age for which there is no labeled dosing recommendation.

Another example where a cross-study comparison is made is antihistamine chlopheniramine. In this case, the peak plasma concentrations are similar, but 80 under the curve for children 6 to 11 is numerically lower compared to adults. And there is no pK data in children less than 6 where there is also no labeled dosing instruction.

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While pseudophedrine and chlorpheniramine pediatric pK data were from NDA submission, brompheniramine pK data presented here is obtained from the literature and has not been reviewed by the agency. Again, cross-study

comparisons show that, on average, systemic exposure in children 6 to 11, as evidenced by 80 under the curve, appears to be numerically less than in adults. Again, there is no exposure data in children less than 6 years of age.

Clearance is one of the most important pharmacokinetic parameters that determine systemic exposure. Here is all clearance data collected across multiple studies in different pediatric age groups compared to adults. Body weight, normalized oral clearance has been found to be relatively greater in children compared to adults. Assuming similar fraction by available between adults and children, this data generally explains the relative exposure of these drugs shown in the previous three slides.

In summary, based on the available pK data, this is what we observed. The recommended label dose in children down to 2 years for pseudophedrine and 6 years for the

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antihistamines chlorpheniramine and brompheniramine generally should not produce concentration above those noted in adults.

The phenomena of postmortem drug redistribution can be a confounding factor towards high postmortem drug concentrations in general. Therefore, it is important to look at some of the distribution, redistribution values of some OTC cough and cold drugs. Generally, postmortem blood sampling was done from the cardiac area, which may not accurately predict the anti-mortem perpheripal blood concentration. The higher the cardiac to perpherial ratio, the higher the postmortem drug redistribution.

Here on the right is the list of cardiac to perpherial ratios available for a handful of OTC cough and cold drugs from the literature. The data shown in the table suggests that this phenomenon can explain up to a maximum of about threefold greater exposure seen in postmortem reports, but it is certainly not enough to account for high postmortem blood levels that were reported in some of the cases.

The factors that influence this ratio are, but not limited to, sight and timing of postmortem blood

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collection, type of biological metrics, sample processing

and the physical/chemical characteristics of the drug such as pK and the volume of distribution.

Now, I'm going to spend some time talking about the pediatric drug development and FDA's current approach. To illustrate that, I'm going t put two comments from the guidances. The ICH E-11 guidance, which is available in your briefing packets, states the pharmacokinetics studies generally should be performed to support formulation development and determining pharmacokinetic parameters in different age groups to support dosing recommendations.

The pediatric pK guidance states, "In general, the pharmacokinetic studies in the pediatric population should determine how the dosage regiment in the pediatric population should be adjusted to achieve approximately the same level of systemic exposure that is safe and effective in adults.

Over the positive pK, the agency has adopted an approach to obtain bridging efficacy data in children using a pediatric study deficient tree based on a good understanding of disease pathophysiology if and only if the following assumptions of similar disease progression

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and similar response to intervention are true, then pK, along with safety, can provide a reasonable path to arrive at pediatric dosing based on systemic exposure.

However, if these two assumptions are not true, then the large efficacy trials, along with safety and pharmacokinetic data would be needed. These would be the type of studies needed if a drug was to be developed for children today and the dose recommendation for children need to be optimized.

So if one has to conduct pediatric pK studies with the objective of optimizing dosing recommendations in children, here are some key considerations for such studies that may include traditional pharmacokinetics with extensive sampling and/or population pharmacokinetic study with sparse sampling.

Single ingredient evaluation would be a preferable method. For the most part, multiple dose evaluation would be preferable, however, single dose evaluation may be sufficient in some cases. There must be an adequate number of subjects within each age group. The exact number of subjects to provide enough confidence in the

estimates would depend upon the variability around
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clearance and the volume of distribution terms. It is preferable to test range of doses to better grasp pK differences across doses, if any.

For younger children, due to obvious difficulty in carrying out studies in that population in general, population pharmacokinetics approach is often employed using sparse sampling strategy. Advanced tools are now available to arrive at optimal blood sampling for the purpose.

Last, but not least, the adequate collection of covariant data is important to identify any significant covariant that impact clearance and volume terms. (Inaudible) pediatric initiatives from the agency have lead to submission of several pediatric pK and safety studies across various therapeutic areas. These studies have lead to critical leveling changes that include unique pediatric dosing. These studies helped focus on drug clearance and its variability in children.

Pediatric dosing is not always obtained by simply applying body weight or body surface area-based calculations to the adult dose. And in the systemic exposure in children is not always predictable based on
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prior adult information.

I will conclude with an example from a recent dose optimization. This is an example of Desloratadine, a second-generation prescription antihistamine. Pediatric dosing is based on achieving similar exposure between adults and children and demonstrating adequate safety in children down to 6 months of age. However, generally, for allergic rhinitis, the assumption of similar disease progression and similar response to intervention are believed to be true.

(Slide)

DR. ROY: Here, traditional pharamcokinetic approach with extensive pK sampling was utilized to arrive at dosing down to 2 years as shown in the table at the top. Below the age of 2 years down to 6 months, pediatric dosing was predicted based on population pharmacokinetic analysis, utilizing sparse sampling strategy. Based on the population mean clearance estimates, the pediatric

dose that would provide a similar exposure as that in adults following a 5 milligram dose was determined to be 1 for 6 months to 1-year-old children and about 1.29 milligram in children 1 to 2 years of age.

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This modeling and simulation exercise allowed the sponsor to arrive at more precise dosing in children down to 6 months. Therefore, the final labeling recommendations for this product reads, "adults and children more than 12 years of age is 5 milligram once daily. From children 6 to 11 years, half that dose and from children 1 year to 5 years of age it's a quarter of the adult dose. And from children 6 months to 11 months, it's 1 milligram once daily."

It is worthwhile to point out here that though the dosing in children down to 2 years mimics the monograph-like fractional dosing algorithm, collection of age-appropriate pK data helped the sponsor precisely define age subgroups and suggest unique dosing in younger children. This is only possible due to the use of advanced pharmacokinetic modeling and simulation tools.

So the bottom line is, if a drug is to be developed today, we do have some advanced pharmacokinetic tools that we did not have 30 years back, which can be employed today to determine pediatric dosing provided we have relevant pharmacokinetic data and safety is ensured.

Finally, I would like to again reemphasize the

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assumptions of the pediatric study just recently. Similar disease, similar intervention between adults and children before pK data can be useful.

So to summarize, overall, there is no pediatric pK data for a large number of OTC cough and cold drugs. Based on the data we have, pseudophedrine, chlorpheniramine and brompheniramine monograph doses do not appear to exhibit greater drug exposure in children relative to adults. As in adults, drug clearance is high variable in children and not readily predictable based on prior adult information.

Among many factors, the two critical factors that impact clearance mechanisms in children are antegy of the clearance process and the genetic polymorphism. The postmortem drug redistribution may partly explain high

postmortem levels in reported cases. So therefore, to conclude, to optimize pediatric dosing of OTC cough and cold drugs, the question for the Committee is should additional pharamcokinetic studies be conducted, and if so, for which ingredients and what ages? Thank you.

DR. STARKE: Good afternoon. I'm Dr. Peter Starke. I'm a pediatrician, medical reviewer and associate

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director for safety in the Division of Pulmonary and Allergy Products. I will be talking this afternoon about the considerations for extrapolation of efficacy from adults to children.

While I will be addressing extrapolation for prescription drug products, the considerations and decision tree used to make decisions regarding extrapolation for prescription products is entirely applicable to the nonprescription products.

(Slide)

DR. STARKE: You see Dr. Lee's name up there. He contributed greatly to this presentation. I just wanted to acknowledge him.

Now, I'll be talking about three areas. First, I'll give a brief background to the regulatory aspects of pediatric use information for prescription drug products, which includes extrapolation to pediatric subgroups. Next, I'll talk about the decision tree for extrapolation. I'll use as an example here Allegra, an antihistamine that was developed for allergic rhinitis and chronic idiopathic endocardia or CIU in children.

As part of this discussion, I will talk about the

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end points we used for allergic rhinitis in clinical trials, both in adults and in older children. And finally, I'll give an example of an antihistamine, Tavist, which was studied for cold indication in patients 12 years of age and older. And this last example may help you understand the sorts of studies that can be performed for cold indication and may help guide your discussions for the nonprescription products.

Now, the need to provide pediatric information and labeling for prescription drugs comes from two pediatric rules finalized in the 1990s. The 1994 Pediatric Final Rule introduced the requirement for pediatric use section

in the labeling and allowed for extrapolation of efficacy to children. The 1998 Pediatric Final Rule required that pediatric studies be performed in appropriate pediatric populations.

Both rules were codified in the Pediatric Research Equity Act or PREA, which was signed into law in 2003. PREA both requires pediatric assessments and allows for extrapolation of efficacy. PREA applies to drugs and biologic products, but it does not apply to the monograph drugs.

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Under both the 1994 rule and PREA, extrapolation of efficacy from adults and older children to younger age groups is acceptable if the course of the disease and the effects of the drug are sufficiently similar in pediatric and adult populations. The parentheses with the wording inserted are from the pediatric rule and is not in PREA.

Extrapolation must be supplemented by dosing, pK and safety data in the appropriate age groups. When extrapolation is not appropriate, clinical studies are necessary. It's important to note that we do not extrapolate safety and we require assessments in all ages. With that said, safety evaluations are primarily performed to confirm the safety findings from adults and older children.

These are the types of factors we consider when we make a decision regarding extrapolation. We consider the course and pathophysiology of the disease process. We also consider the lower bounds of the disease process. That is, the point at which one can generally identify the disease as a distinct biologically plausible entity. We also consider the immune maturation response; anatomical differences as well mechanism reaction and response to the

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drug.

Other factors we consider are our experience with a particular drug, drug class and indication. For many of these drugs, for example, antihistamines for allergic rhinitis we have a vast amount of experience with the drug class and indication, understand the pathophysiology of the disease process and mechanism of action of the drugs and will have had experience with the same drug that's been studies already in the adult setting. We also take

into account whether the activity of the drug is via systemic or local mechanism and I'll go into this more in the next slide.

Finally, we take into consideration our overall estimate of the balance between efficacy and safety, taking into consideration the particular indication and drug at hand.

(Slide)

DR. STARKE: As I mentioned, extrapolation of the efficacy depends, to some extent, upon whether the drug is systemically or locally active. Systemically active drugs have measurable drug concentrations in the blood and the blood is the relevant viral space, pK data then allows the

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estimation of the dose based on adult data as you've heard already; and examples of these include all the products under your consideration today.

In contrast, locally active drugs may have concentrations that are measurable in the blood, but blood is not the relevant bio-space. For products submitted to our division, the relevant bio-space is either the lung or the nose. But obviously, if we were talking about a topical drug, it would be the skin. For drugs, pK is important as an estimation of systemic safety, but pK data cannot be used for an estimation of the dose. And of course, the examples for our division are the intranasal and orally inhaled products.

Now, it's important to realize that for locally active drugs, the size of the efficacy and safety database in children necessarily increases and is often substantial because the appropriate dose for children cannot be estimated from comparable systemic exposure to that in adults.

An example of such a program is Pulmicort respules. We had already approved Pulmicort tubuhaler, which is Budesonide dry power formulation intended for maintenance

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treatment of asthma in patients 6 years of age and older. Pulmacort rescules is the nebularization formulation intended for young children. Drug development included three large studies with an expose of over a thousand children, exploring the appropriate dose for a range of asthma severities.

(Slide)

DR. STARKE: Now, this slide just acknowledges the many difficulties with performing studies in children. Of particular relevance are the subject end points that often must be used supplemented by objective end points when available and appropriate. Even in adults, subjective end points may be problematic and for children, subjective end points, particularly, in the youngest age groups may be particularly problematic, as they may need to be assessed by a caregiver.

My division has accepted extrapolation using extrapolation for a number of conditions. Here I'm showing the extrapolation for allergic rhinitis and chronic idiopathic pericardia as this will be an example that I'll come back to in just a minute, and it's particularly applicable to your deliberations. For

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seasonal allergic rhinitis, we've extrapolated down to 2 years of age, for perennial down to 6 months and for CIU down to 6 months as well.

It's important to note here that for allergic rhinitis and for CIU, the biology of the disease is extremely well established. The allergen effect on the mass cell, degradulation, release of histamine and the effects of histamines on coastal tissue are well understood. Similarly, the effect of an antihistamine on these processes has been extremely well documented.

Now, the last bullet on this slide is not quite correct, so let me just explain what I mean. It's not that we have not made a decision. Rather it's that we have not had any applications to our division, so we have no experience with extrapolation for the common cold.

So this slide illustrates what we ask for in allergic rhinitis, although it's also applicable to all systemically active drugs. While there are topically active drugs administered to the nose, I'm really focusing on a systemically active drug here, the differences primarily being in establishing the appropriate dosages for children as well as providing more data to support

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efficacy and local safety.

(Slide)

DR. STARKE: Now, this slide doesn't fully capture

what we do for allergic rhinitis. Efficacy and safety have generally been established in adults and children first, although for some the development programs in adults and children may be concurrent or overlap. We ask for pK to establish the dose as well as safety evaluations in all age groups. We ask for efficacy down to age 12 and we will extrapolate efficacy below age 12.

However, we generally ask for supportive efficacy data from the safety study in older children if they can score the symptoms. And we may also ask for some pK data in that safety study. Both the pK and the efficacy trends are measures that help us assure adequate compliance in a safety study.

Now, a word about how we do these studies of the scoring that we typically use for allergic rhinitis. We typically ask for patient-assessed symptom scoring for allergic rhinitis and typically, we ask for at least four sets of symptoms to be assessed, including rhinorreha, nasal congestion, nasal itch, and sneezing. Other

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symptoms such as non-nasal symptoms are often assessed as well.

We ask for assessments to be performed on a symptom severity scale. The preferred scale being show on the slide on a 4-point scale where zero is no symptoms and 4 is the worst severity for that particular symptom. But we have seen and have accepted other scales as well.

Assessments are made by patients over the entire course of the treatment period, generally, two weeks for SAR or seasonal allergic rhinitis and four weeks for PAR or perennial allergic rhinitis. We ask that the scoring be performed at the end of the dosing interval and recorded in a symptom diary over the entire course of the study. This, of course, means that we already have information about the drug and the appropriate dosing interval.

We also ask for the studies to collective both reflective and instantaneous scoring. Reflective scoring asks the question how severe has that symptom been since the last dose of study treatment? Instantaneous scoring asks the question how is my symptom at this moment?

(Slide)

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