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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 19, 2007

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C O M M I T T E E M E M B E R S

Mary Tinetti
Darrel Lyons
Laura Marcia Rappley (Telephonic)
George Goldstein
Elizabeth Garofalo
Richard Gorman
William Calhoun
Tom Newman
Mike Cohen
Prescott Atkinson
Jesse Joad
Robert Taylor
Marie Griffin
Jan Hewitt
Will Shrank
Ralph D'Agostino
Ben Clyburn

Ruth Parker
Dennis Bier
Avital Cnaan
Richard Neill

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Amy Celento
Robert Daum
Leon Dure
Jeff Rosenthal
Sean Hennessy
Ann McMahon
Joel Schifferbauer
Charlie Ganley
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S P E A K E R S

Robert Temple
David Bromberg
Winnie Landis
Patricia Jackson Allen
Peter Lurie
Daniel Mannello

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P R O C E E D I N G S

MARY TINETTI: Let's get started.

LAURA MARCIA RAPPLEY: Laurie.

MARY TINETTI: I'm going to read the statement that I read yesterday morning.

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.

LAURA MARCIA RAPPLEY: Laurie?

MARY TINETTI: Anybody know who that is? I believe that's Dr. Rappley saying hello, she's joining us by phone today.

We look forward to a productive and interesting meeting. In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the Advisory Committee

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members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however FDA will refrain from discussing the details of this meeting with the media until its conclusion. A press conference will be held in the Distance Learning Room 9232 immediately following the meeting.

Also the Committee's reminded to please refrain from discussing the meeting topic during

breaks or lunch, thank you.

We're now going to ask the Committee to introduce themselves. Again, just state who you are, where you're from and what you're representing and I'm Dr. Mary Tinetti from Yale University, internist in geriatrics and I'm chairing the Committee.

Dr. Laura Marcia Rappley who is from the Pediatric Advisory Committee is joining us by phone and that's who you've heard before and you'll be

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hearing her throughout the day. We'll start with Dr. Goldstein.

GEORGE GOLDSTEIN: George Goldstein, industry liaison representative and pediatrician.

ELIZABETH GAROFALO: Elizabeth Garofalo, the industry representative to the Pediatric Advisory Committee. I'm a pediatric neurologist and a pharmaceutical consultant.

RICHARD GORMAN: Richard Gorman, a pediatrician representing the professional health care organizations through the Pediatric Advisory Committee, a non-voting member.

WILLIAM CALHOUN: Bill Calhoun, I'm an internist allergist, pulmonologist from the University of Texas Medical Branch in Galveston.

TOM NEWMAN: Tom Newman, I'm a general pediatrician and professor of epidemiology and biostatistics in pediatrics at UCSF and a member of the Pediatric Advisory Committee.

MIKE COHEN: And I'm Mike Cohen, I'm a pharmacist with the Institute for Safe Medication Practices and our area is medication safety and

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medication or prevention.

PRESCOTT ATKINSON: I'm Prescott Atkinson, I'm an associate professor of pediatrics at the University of Alabama in Birmingham and I'm Board certified in allergy and immunology.

JESSE JOAD: I'm Jesse Joad, I'm professor of pediatrics at University of California at Davis and I'm Board certified in allergy and in pediatric pulmonology.

ROBERT TAYLOR: I'm Robert Taylor, I'm from Howard University College of Medicine where I'm professor of pharmacology in medicine. I'm an internist and clinical pharmacologist and member of the Nonprescription Drug Advisory Committee.

MARIE GRIFFIN: Marie Griffin, I'm an internist and pharmacoepidemiologist at Vanderbuilt and I'm a member of the Nonprescription Drug Committee.

JAN HEWITT: Jan Hewitt, I'm the consumer representative for the NonPrescription Drug Advisory Board, I'm at the University of Michigan, I'm the director of the IRB there.

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WILL SHRANK: Will Shrank, I'm an internist in the division of pharmacoepidemiology and pharmacoeconomics at Brigham and Women's Hospital at Harvard Medical School.

RALPH D'AGOSTINO: Ralph D'Agostino, biostatistician from Austin University and a member of NDAC.

BEN CLYBURN: I'm Ben Clyburn, I'm an internist from the Medical University of South Carolina, a member of NDAC.

RUTH PARKER: Ruth Parker, I'm an internist at Emory University School of Medicine, also Boarded in pediatrics, health literacy.

DARREL LYONS: I'm Darrel Lyons, the designated Federal official for the Nonprescription Drug Advisory Committee.

DENNIS BIER: I'm Dennis Bier, a pediatrician from Baylor College of Medicine and I'm on the Pediatric Advisory Committee.

AVITAL CNAAN: I'm Avital Cnaan, I'm a biostatistician from the University of Pennsylvania and Children's Hospital of Philadelphia and I'm on

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the Pediatric Advisory Committee.

RICHARD NEILL: I'm Richard Neill, I'm a residency program director and vice chair of the Department of Family Medicine and Community Health at the University of Pennsylvania.

AMY CELENTO: I'm Amy Celento, patient

representative to the Pediatric Advisory Committee.

ROBERT DAUM: Good morning, I'm Robert Daum, I'm a pediatrician, professor of pediatrics infectious disease guy, the University of Chicago.

LEON DURE: I'm Leon Dure, the professor of pediatrics and neurology at the University of Alabama at Birmingham. I'm on the Pediatric Advisory Committee.

JEFF ROSENTHAL: And I'm Jeff Rosenthal, I'm a pediatric cardiologist and epidemiologist at the Cleveland Clinic and I'm a member of the Pediatric Advisory Committee.

SEAN HENNESSY: Good morning, I'm Sean Hennessy, I'm an pharmacoepidemiologist at the University of Pennsylvania.

ANN McMAHON: Ann McMahon, pediatrician,

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I'm representing the Office of Surveillance and Epidemiology at the FDA.

JOEL SCHIFFERBAUER: Joel Schifferbauer, Deputy Division Director in the Office of Nonprescription Products.

CHARLIE GANLEY: Charlie Ganley, the Director of the Office of Nonprescription Products, FDA.

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

DARREL LYONS: Before I read the conflict of interest statement, I want to again remind everyone to silence their cell phones if you have not already done so and also I would like to identify the press contacts, we have Susan Cruzan, Christopher Kelly and Rita Chapelle.

The Food and Drug Administration is convening today's joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With

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the exceptions of the industry representatives, all members and consultants are special Government employees or regular Federal employees from other

agencies are, and are subject to Federal conflict of interest laws and regulation.

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

FDA has determined that members of -- excuse me, members and consultants of these Committees are in compliance with Federal ethics and conflict laws of interest. Under 18 USC 208, Congress has authorized that FDA to grant waivers to special Government employees who have potential conflict of interests when it is determined that the Agency's need for a particular individual's services outweigh his or her potential conflict of interest. Under 712 of the Food, Drug and Cosmetic Act,

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Congress has authorized FDA to grant waivers for special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committees essential expertise.

Related to today's discussions, the -- related to the discussions of today's meeting, 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 USC 208, their employers.

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

Today's agenda involves discussion 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

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will be discussed.

Based on the agenda for today's meeting, all financial interests reported by the Committee members and consultant, conflict of interest waivers have been issued, in accordance with 18 USC 208 V3 and 712 of the Food, Drug and Cosmetic Act, to Dr. Ralph D'Agostino for his duties on a data safety monitoring board on an unrelated study for an affected firm. Dr. D'Agostino receives between 10,001 and 50,000 dollars per year for his services. This waiver allows Dr. D'Agostino to participate fully in today's deliberations.

FDA's reason for issuing the waivers are described in the waiver documents which are posted on FDA's Website at www.FDA.Gov back slash OHRMS back slash dockets back slash default .hto.

Copies of the waivers may be also obtained by submitting a written request to the Agency's Freedom of Information Office, Room 630 of the Park Lawn Building. A copy of this statement will be available for review at the registration desk during this meeting and will be included as

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part of the official transcript.

Dr. 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 member of Sterling Drugs, Incorporated.

Dr. Garofalo is employed by 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 participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the Committee of any financial relationships that they may have with any firm at issue.

MARY TINETTI: Thank you, Darrel.

We're now going to move on to the open public hearing component and we'll have six speakers

and we just remind you, number one, to talk into the mic and, number two, to stick to your time

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allotment. The first speaker will be Dr. Anthony Temple who is a consultant who will be speaking with us on pediatric dosing.

I'm sorry, I have to have an open public hearing statement first, of course.

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

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with a sponsor, its product and if known, its direct competitors. For example, this financial information may include a sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting. Likewise, FDA

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encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and its Committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when

recognized by the chair. Thank you for your consideration.

So with dignity and courtesy, Dr. Temple.

ROBERT TEMPLE: I was told that there

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was a clicker to advance slides, but there's nothing here.

Short people always have trouble with microphones.

Okay. Well thank you. I appreciate this opportunity to present here today. I've been asked to point out that I am here representing myself, but for your information I'm a pediatrician and a clinical pharmacologist, toxicologist with interest, I was a faculty member at the University of Utah College of Medicine for eight years and did general pediatrics in poison control and then spent 26 years working for McNeill consumer health care, the makers of Tylenol and Motrin. I retired in 1995, I do still consult with them.

Now if I can get this to work. The purpose of this presentation is to encourage the Advisory Committees to endorse the use of a pediatrics dosing schedule that has narrower age ranges and an additional age-, weight-related schedule. I also want to seek an endorsement from the Committee that dozing information should be

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placed on all consumer labels for all ages for which the product will be used.

It is a real public health matter to get dosing on the label for parents.

What I present today is not new. In fact, it has been submitted or presented to FDA many times over the past 22 years. I was 44 years of age when I first presented this information to FDA. I'm now 67 and not getting any younger.

You heard yesterday a lot about the 1976 proposed rule for cough, cold allergy, bronchodilators, anti-allergy products and I'm not going to go through the history because it was done quite well by FDA, but at that, at that -- in that

document age-related schedules were created that are ages 2 through 5 and 6 through 11.

Every one of the FDA staff positions papers has talked to you about this and you've heard a lot about it, but you've heard little about the alternative dosing schedules in the OTC marketplace except from Dr. Chang.

In 1982 a pediatric dosing schedule for

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Acetaminophen was implemented. It involved the use of narrower age breaks and, as proposed previously for aspirin, and added a weight-based schedule that allowed the dosing to be more precise.

So in 1985 following the issuance of proposed rules for cough and cold products we arranged a public meeting with FDA staff. Those minutes are publicly available. At that meeting we discussed in great detail the concepts of a new dosing schedule and proposed that the Agency adopt the new pediatrics dosing schedule for cold, cough and allergy products.

Subsequently in submissions to the TFMs and in response to an FDA's notice of intent published in 1988, we continued to propose the new pediatric dosing schedules. In those submissions we also argued that labeling for all cough, cold ingredients should be contained -- I'm sorry, should contain dosing information down to age 2, that would be even for antihistamines and that FDA should adopt professional dosing below age 2 so that health care professionals should have consistent information and

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products should be consistently dosed.

However, when the antihistamine final monograph issued in 1992 and the nasal decongestant final monograph issued in 1994, the decision about pediatric dosing was deferred. In 1995 an NDAC meeting was held to discuss pediatric dosing about DC medicines. I again presented at that NDAC. That NDAC voted unanimously in favor of the improved dosing schedule where it could be applied. That's 12 years ago.

But this is where we still are some 12,

some 22 years later. And what I want to do is describe the problem with the current dosing schedules and define how an improved schedule would be a benefit even in the face of our seeking new pk and clinical data that might eventually lead us to make some adjustments in a dosing schedule. We typically talk of drug doses in milligrams per kilogram, which is what I'll do. What happens when the doses children get -- what the dose children get with the current schedule are administered using approved, overly wide dosing ranges, the average

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size child who is 11 and a half years old will get a dose that is one half the dose that a 6 year old will get on a milligram per kilogram basis. If you compare the 10th percentile 6 year old with the 90th percentile 11 and a half year old, there's a three-fold difference in doses.

Another way to think about this is that if the dose for an average 50th percentile 6 year old is .5 milligrams per kilogram, then the dose for an average 50th percentile 11 and a half year old is only 2. -- .26 milligrams per kilogram and the dose for a very large 90th percentile 11 and a half year old is .2 milligrams per kilogram.

So, is the pediatric dosing schedule approach currently being used for most oral OTC medicines including cough and cold medicines an adequate method? Not really.

A much more preferable schedule would be one with narrower age breaks and even better a weight schedule defined for OTC product use. Over the years I referred to this as dosing based on the concept of a standard pediatric dosing unit. What

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this means is that you can define specific age ranges and weight ranges that go up in steady increments that would be consistent with specifically defined increases in a standard pediatric dosing unit for a given product which could be defined for any OTC ingredient.

Right now it's used, they are fractions of 1/8 of the adult dose because that worked best

for the age-related schedule when it was conceived and works well with the weight schedule. We have used this schedule now for nearly 25 years with Acetaminophen and on Ibuprofen products. This figure provides a graphic representation of why this schedule with more narrow age breaks provides more consistent dosing.

As it turns out, using either the new schedule I'm proposing, I have been proposing or the old, the current schedule, the 6 year old dose gets the same. This 6 year old dose is also the highest dose on a milligram per kilogram dose that is given during the course of the schedule and is essentially the same as the 12 year old dose.

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To provide general applicability of this approach, doses for all the other ages have been adjusted to be a proportion of the dose given to a 6 year old by setting a dose/weight ratio equal to one for the 6 year old and then less for the rest and that's how you see it proposed.

Using the current schedule, the dose of a 5 year old is just half that of a 6 year old, for a 5 and a half year old is just half that of a 6 year old, as is the dose for an 11 and a half year old. With the proposed schedule, trough doses are not nearly so low and more of the doses lie within a tighter age range.

But this is the even better schedule. This figure represents dose/weight ratios for the weight-related dosing schedule, with a weight schedule, the peak to trough doses lie within an even tighter range.

Most of you are probably familiar with Acetaminophen. Here is what happens when you use the 80 milligram SPDU for Acetaminophen. Just as we are trying to achieve, the doses generally fall

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within the 10 to 15 milligram dosing range. It's even more precise with the weight-based schedule.

Would I apply this schedule given the various, to the various cough and cold ingredients given the amount of clinical data currently

available? Yes, I would, it's better than the current schedule.

Of course we do have pk data that show potential for extrapolation to children, of doses to children 2 to 11 years for pseudoephedrine and ages 6 to 11 for chlorpheniramine and this slide shows the dosing ranges provided for chlorpheniramine by the proposed new schedule compared to the current and this slide shows the dosing range provided for pseudoephedrine by the current and proposed new schedules.

This is the same pattern you would see for any cough, cold ingredient or any other orally administered medication. Of course the question can be asked if you tighten up the dosing schedule, would you dose more children in an effective range or not.

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Oops, I'm sorry. A study conducted in 2004 by Ian Paul and colleagues is instructive. This is the same study referred to by the sponsors, the industry and FDA during this meeting but from a different subset of that data. Paul and colleagues studied children ages 2 through 11 using current OTC doses of Dextramethorphan and the wide age range schedule in a monograph.

When they analyzed their data with regard to symptom control, they reported a dose range effect. Subjects who received doses of .35 to .45 milligrams per kilogram were less likely to have symptom control than those receiving doses of .45 to .6 or .6 and above.

While the authors did not analyze the degree of symptom control by age, it's very likely that the oldest and heaviest children in this, these wide age ranges, were getting the less effective doses.

This figure from their study shows the measured parameters for each of the three dosing levels. I should point out that because of the

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small numbers of enrolled subjects and a modest effect size, they did not show statistical

significance between groups, but there is a clear trend. These data argue to me that there is a benefit to the higher dose range and to providing a dosing schedule that keeps the doses relatively higher.

This slide shows the dosing range provided for Dextramethorphan by the new proposed dosing schedule and it is in that higher range.

So, if we want a better way to approach dosing, I believe it should be the standard pediatric dosing unit because it can be applied consistently to OTC ingredients and having a common schedule would allow each ingredient to be given in a more consistent milligram per kilo dose and when given in combination would allow all of the ingredients to be properly dosed, even with standardized delivery devices and concentrations.

Next point. In their response to the FDA request for comment, AAP made the following statement. Appropriate labeling should reflect

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accurate dosing information so that children's health care providers can make an informed decision as to whether or not to recommend use of these products and counsel parents appropriately should they choose to do so.

Oh, it just went dead. Did I do that? At least that's one element of the letter with which I'm in agreement. You heard a lot about adverse event reports and fatal cases for these categories of drugs since yesterday. Many suggestions have been postulated as root causes for the misuse cases that occurred. One root cause that was alluded to by FDA but not really discussed is the lack of dosing information on the label for children, particularly under age 2.

Importantly, the vast majority of cases of misuse occurred in that under 2 year age range. None of the products intended for use in children have been allowed to have dosing for children under age 2 on the label and also elevated were AEs for antihistamines between age 2 and 5 where there is no dosing information on the label for parents. So

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when parents use these products in children in these age ranges, they have to seek professional guidance or -- on dosing from a physician or pharmacist and too often apparently that communication just doesn't work.

These facts suggest to me that withholding of dosing information from the label may well have been the most significant contributing factor to the cases of misuse. Past Advisory Committees have argued that keeping the dose off the label would be a way to force parents to call their physicians. FDA has implemented that policy. It hasn't worked. I believe it's time to get the correct dosing information for children on the label.

I think that a reasoned approach would be, to labeling is that the consumer labeling should contain dosing information for children in each and every specific age group the drug is to be used in. We must not let the concern about a likelihood of use without consulting a physician override the risk of misuse if consumer dosing information is not

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provided. Even if the label contains language like do not use until a physician has been consulted, it should contain dosing information anyway.

I'm concerned that without a strong signal from the Committee, the FDA will not put dosing information on the label for all age groups. You know, it's been over 10 years since NDAC recommended that dosing information for children under 2 be placed on Acetaminophen products and the Agency still has not allowed us to do so. Now that's a public health issue.

In conclusion, the NDAC should endorse once again the use of dosing schedules based on more finely-divided age breaks with inclusion of and emphasis on the addition of the proposed weight schedule. New pk and efficacy data should be obtained to refine doses, but the new dosing schedule should be adopted while new scientific studies are undertaken. This would be a real public

health benefit.
The NDAC should endorse the placing of dosing information on the consumer label for all age
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ranges in which the product will be used. Do not use the excuse that since you want the consumer to call the doctor you would not give them access to correct dosing information. The dose should be on the label and these products should be available.
Thank you.
MARY TINETTI: Thank you, Dr. Temple.
Next is Dr. David Bromberg from the American Academy of Pediatrics.
DAVID BROMBERG: Short but not quite that short. I have no financial disclosures.
Thank you for the opportunity to provide comments to the Pediatric Advisory Committee and the Nonprescription Drug Advisory Committee of the Food and Drug Administration.
My name is Dr. David Bromberg and I'm a pediatrician with 30 years of clinical experience treating children in a private practice in Frederick, Maryland. It is in this practice that I care for children with cough and colds on a daily basis and address the issues of cough and cold medications with my patients and their families.
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I'm here today in an official capacity representing the American Academy of Pediatrics.
Cough and colds bring a lot of children to medical attention either in the office or over the phone. Parents want to know what they can do to give their children relief. The conversation quickly turns to one of the multitudes of commercially-available cough and cold preparations. These compounds were never studied in children prior to approval, rather efficacy data in adults were extrapolated to children. When these drugs were approved, that was the standard practice.
This extrapolation was based on the assumption that children are little adults, but since that time our understanding of the physiology of children and how they absorb, metabolize, excrete

and react to medication has evolved to the point where we have ample evidence to state that children are, in fact, not little adults. The data generated from the implementation of the Best Pharmaceuticals for Children Act, the BPCA, and the Pediatric Research Equity Act, the PREA, humble us on a

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regular basis.

There is much we still do not understand about the difference between children's and adults' drug metabolism and action. Although cough and cold products were originally approved based on data extrapolated from adults and applied to children, subsequent studies have found these products to be ineffective in children under six years of age.

Based on the evidence available in peer reviewed literature, these medications either singly or in combination do not work to relieve cough and cold symptoms in this population. Reports that have been received by the FDA point to a possible risk of death and other adverse events from the use and misuse of cough and cold products in children, especially in, but not limited to, children younger than 2 years of age.

The American Academy of Pediatrics urges the FDA to pursue further studies to determine whether or not cough and cold products have any beneficial role in the treatment of what is, in fact, a self-limited disease in children, the common

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cold.

Simple, simply labeling these products with a warning against use in children under age 2 years is part of a solution, but not the whole solution. While it is important to limit the use of these products in this especially vulnerable population, such labeling does not go far enough or address the use of cough and cold medications in older children. Why not label these products with what we actually know. In children under 6 years there is direct evidence that cough and cold products do not work, and some indirect evidence that cough and cold products present a risk.

AAP advises that appropriate and consistent labeling regarding the lack of efficacy and potential side effects for cough and cold products be developed and adopted by all manufacturers of these products.

AAP proposes the following labeling language, quote, "This product has been shown to be ineffective in the treatment of cough and cold in children under 6 years of age. Serious adverse

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reactions including, but not limited to, death have been reported with the use, misuse and abuse of this product," end quote.

With this type of labeling in place, the American Academy of Pediatrics would urge the FDA to pursue further studies to determine whether or not cough and cold products have any beneficial role in the treatment of the common cold and the simple cough.

The Academy would urge the study of single ingredient formulations first followed by studies of any proposed or marketed combination product. The AAP has spoken with a single voice for over 30 years regarding the importance of studying medicines in children. If a medicine will be used in children, it should be studied in children. Cough and cold medication should not be exceptions to this rule.

While troubling to parents and children, cough and cold symptoms are usually benign and often self-limited. The available data show cough and cold products to be ineffective for children under

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6 years with cough and cold symptoms.

In the absence of evidence of efficacy, any risk associated with these drug therapies is unacceptable. The current labeling of these products is, therefore, inadequate, inaccurate and dangerous. With labeling that follows the Academy's recommendation, pediatric data can continue to be generated and the wording of the labels can then be modified to reflect increased understanding about the safety and efficacy of cough and cold products.

On behalf of the American Academy of Pediatrics, I thank you for your attention.

MARY TINETTI: Thank you, Dr. Bromberg. Next is --

CHARLIE GANLEY: Dr. Tinetti.

MARY TINETTI: Yes.

CHARLIE GANLEY: Yeah, could I just ask a question for clarification from him because we had a question based on the information that they had submitted.

Is to just clarify what is your position -- what's the AAP's position on what is

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adequate data, is it pharmacokinetic data or is it clinical efficacy data?

The second question you've limited it to, yes, less than 6 years of age, yet the data that we saw yesterday included children in the 6 to 11 year age range, so why wouldn't that warning apply also to the total population of children under 12 years of age?

The third question is whether, you know, most of the prescription products that have a decongestant and are based on the acceptance that the decongestants work, so are you applying this also to prescription products that may have a decongestant in it?

DAVID BROMBERG: The Academy's position is that both the efficacy and pk data should be obtained in children and that the efficacy should be studied in controlled trials of these products in children at different ages.

I can't remember all of the questions and I'm not, I'm not a pharmacologic -- I'm not an expert in pharmacology, I'm a clinical pediatrician.

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CHARLIE GANLEY: No, but the data we saw yesterday enrolled children, you know, up to 12 years or even past 12 years of age and, but you're cutting it off at 6 and I don't understand that cutoff, if the, if there's a lack -- the same type of lack of efficacy data exists for the 6 to 12 year age range, why wouldn't we just label all

these products as you have suggested so that they're not available at all for children?

So that's the, there has to be a certain logic for us to understand why you've cut it off at 6 and why it wouldn't apply to everyone.

DAVID BROMBERG: I'm not sure why the decision was made. You know, I think there's a step-wise approach and I think we're looking at improving labeling and I think that the Academy feels at this point that the recommendations that they've suggested would improve the safety for children in the ages, as the ages mentioned and I think the dangers for the older children are somewhat less and somewhat less of a pressing issue.

CHARLIE GANLEY: But there's still a

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lack of efficacy there, if I understand your argument, so if there's a lack of efficacy there, why wouldn't we say that? I'm sure if we looked at the data on 6 to 11 years age group we're going to find serious adverse event reports in that age group, they may be a smaller number, but they're still there and based on the presentations yesterday from the petitioner that any adverse events with lack of efficacy, that those products should not be available for children.

DAVID BROMBERG: My understanding is that the efficacy data is unclear at this point and I think the Academy is going to protect the majority of children that it can at this time and that the recommendations would then be to do the labeling on under 6.

CHARLIE GANLEY: Okay.

JOHN JENKINS: Could I ask one other follow-up question, is the Academy's position, does that carry over to all drugs for children?

You're suggesting that we have to have efficacy data for the cough cold indication, does

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that carry over to all pediatric indications?

That seems to be a real change in position. The pediatric rule and the foundation of our pediatric development programs for the last 15

years has been about extrapolating efficacy when it makes sense, we don't extrapolate the dose, we don't extrapolate the safety and we don't extrapolate the risk benefit, but we have in certain cases extrapolated efficacy. It seems now the Academy is saying we don't want to do that anymore; is that your position?

DAVID BROMBERG: No, I think that the Academy doesn't want to create therapeutic offerings for children and I think that the Academy is clearly, what it's clearly stated over the years is that drugs need to be, drugs used in children need to be studied in children. I think that's the simple clear message and I think we continue to hold that position.

MARY TINETTI: Thank you, Dr. Bromberg.

Next is Winnie Landis from the American Pharmacists Association.

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WINNIE LANDIS: Good morning. I am Winnie Landis, a community pharmacist and diabetes educator with CVS Pharmacy in Lafayette, Indiana.

I'm here today representing the profession of pharmacy as President of the American Pharmacists Association.

APhA is the first established and largest professional pharmacy organization with over 60,000 members who provide care in all practice settings. Improving the public's health and safety with respect to medication use is the pharmacists and APhA's highest priority. Pharmacists, the medication experts on the health care team, are the most accessible health care providers and the only health care provider available to interact and communicate with consumers at the point of sale for prescription and OTC products.

APhA's comments will focus on the pharmacists' role in helping parents and care-givers select and use appropriate OTC products for pediatric patients, specifically we recommend the following. The need for a complete, comprehensive

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and understandable labeling information, removing

risks of the same brand name or brand name line extensions being used for OTC products containing different active ingredients, include the statement on OTC products ask your doctor or pharmacist about the directions for using this product and also the statement do not use in children under 2 years of age, a standardization in OTC dosing units, improvements to the OTC drug monograph information and also pharmacists representation on FDA Advisory Committees that address OTC products.

Pharmacists rely on the FDA to determine whether medications, including OTC products, are safe and effective for their patients. However, we applaud our colleagues at the nonprescription pharmaceutical product manufacturers for proactively responding to reports of improper use of these products, some of which have led to overdoses.

Pharmacists offer a value-added component to OTC products assisting an appropriate product selection, identifying potential dangerous combinations of medication and educating patients on

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the proper use of these products. The proximity of OTC products to pharmacists along with the knowledge that pharmacists have allow us to play a critical role in consumer selection and purchase of OTC products, or determining when the patient needs to be referred to another health care professional.

Pharmacists also calculate appropriate doses based on age, weight, symptoms and provide training on the proper use of measuring devices to be used with some medications. In some cases pharmacists may recommend not to use certain products based upon the patient's needs.

The absence of pediatric specific formulations and dosing guidance led to APhA's support of FDA's efforts to require manufacturers to include more extensive studies in the pediatric population for both prescription and OTC products. A large portion of the issue we're discussing today reflects on a need for clear and comprehensive information about the safe use of these products.

The label on the package is the primary

vehicle used by consumers to obtain information
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about using these products. We agree with the concern raised by the FDA and other stakeholders that improvements to the packaging label are necessary. APhA supports the use of labeling that includes complete, comprehensive and understandable information that is not misleading. The label should also inform consumers of the potential benefits and risks of the product, especially if used in pediatric populations as well as cautionary statements if used for a specific pharmacological effect such as intentional sedation.

We also recommend that the FDA clarify and improve current labeling for OTC products used for the pediatric population given the recent challenges with misuse and dosing problems associated with pediatric cough and cold products reported due to the misleading product labeling.

APhA also shares the public's concern about the increasing number of OTC products and the appropriate use of these products. Consumers are challenged to decipher the labeling information and choose from a myriad of products. The complexity is
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compounded by some products whose active ingredients have changed but the product name remains the same or products with the same ingredients but different labeling.

To help consumers make better informed choices, APhA supports disclosure of all therapeutically-active ingredients of an OTC product to the public and discourages the use of the same brand name or brand name line extensions for OTC products containing different active ingredients.

We also recommend that the FDA require labeling on OTC packages to say ask your doctor or pharmacist about the proper directions to use this product, especially when used in pediatric populations. And we also support the recommendation of the Consumer Health Care Products Association to change the labeling on all OTC cough and cold products to read do not use in children under

2 years of age.

In addition to providing consumers clear labeling information, more needs to be done to educate consumers about medication use in general.

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Consumers must be reminded that any medication, including OTCs, has the potential to cause harm if used incorrectly.

Patients may unintentionally exceed the recommended dose by taking the wrong dose of medication or taking multiple products with the same active ingredients.

For the pediatric population, this can occur when parents or care-givers accidentally give the wrong dosage because they use a measuring device incorrectly or determine the dose based on the child's age rather than weight or when they are not aware of similarities among products.

Many products, especially those with multiple ingredients, are particularly challenging for consumers to self-manage. To address this problem, parents or care-givers must be encouraged to read product labeling to understand how to give the medication correctly and to be aware of the possible side effects and what to avoid when administering the medication.

Again, pharmacists are available to help

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consumers learn how to appropriately select and use OTC products, a key to reducing product overdosing, emulated adverse events and equally as important when not to use OTC products, a common recommendation for a pediatric patient.

Unfortunately, despite a recommendation from a physician or pharmacist not to use a cough or cold product in children under 6, parents do give such medications out of desperation to do something to address their child's health care needs. This is a patient safety issue which may be more common than we might like to admit.

Improvement in OTC labeling would better educate parents and care-givers on how to appropriately use OTC products for the pediatric

population.

Another improvement would be to eliminate the use of different dosing units on OTC packaging. For example, some products use the unit teaspoon while others may cause confusion by using units of milliliters or cubic centimeters. APhA recommends that the FDA consider standardizing

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dosage unit terminology to reduce confusion that may contribute to product dosing misuse.

In addition to educating consumers, we encourage the FDA to continue developing ways to better educate all stakeholders, including product manufacturers, pharmacists and physicians about the appropriate use of OTC products. APhA supports efforts to re-evaluate and improve patient safety information provided in all OTC drug monographs.

In addition we also urge the FDA to consider pharmacists for appointment to FDA Advisory Committees that address OTC medications.

Finally, we're looking forward to working with the Consumer Health Care Products Association to educate pharmacists and consumers about the safe and effective use of OTC medication.

In conclusion, we recommend that the FDA consider ways to improve OTC labeling by requiring full disclosure of all active ingredients in OTC products, by taking steps to reduce name and ingredient confusion and by requiring language that these products should not be used in children under

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the age of 2.

We also recommend standardization of OTC dosing units, improving OTC drug monograph information and the importance of having a pharmacist on the FDA Advisory Committee related to OTC products.

Again, pharmacists are available to help consumers use medications appropriately and safely in order to reduce product misuse. APhA has increased communication to its members regarding this issue and we offer our support and assistance in helping the FDA and other stakeholders to educate

the public on this important issue.
Thank you for your consideration of the views of the nation's pharmacists.
MARY TINETTI: Thank you.
Next is Patricia Jackson Allen from the National Association of Pediatric Nurse Practitioners.
PATRICIA JACKSON ALLEN: Good morning, thank you very much. As a pediatric health professional, I applaud the recent decision by many

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of the pharmaceutical companies to withdraw from the market the cough and cold preparations marketed in packages for use in infants and children under 2 years of age. I believe this will result in fewer unintentional overdoses of these medications in children.
But as a health professional, I question the use of cough and cold preparations in children at all. Over 2 billion dollars a year is spent in the United States on more than 800 medications marketed for the treatment of cough and colds, most of them OTC, and most of these multiple drug preparations are a combination of decongestant, antihistamine, cough suppressants and anti-pyretics, increasing the risks.
Many of these medications were first introduced into the market many years ago and did not have rigorous testing on children to determine appropriate dosage or to determine untoured side effects and adverse reactions. I question whether or not these medications would meet the criteria for approval by the Federal Drug Administration for the

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current three-phase investigational new drug process if brought forward today.
Although OTC medications are marketed heavily as effective and safe even in young children, randomized double blind or placebo control studies do not find their efficacy to be greater than that of placebo. Systematic review of OTC cough and cold medications in children conclude these medications have little benefit in controlling

symptoms. Even the use of antihistamines which have been found to have effectiveness in adults with chronic cough have not been found to be effective in children with non-specific cough, i.e., the cough most often associated with the common cold.

In 2006 the American College of Chest Physicians reviewed the research on cough management in children and adults and recommended that children with cough should not be treated with cough suppressants or other OTC cough medications as these medications have not been shown to be efficacious.

A wide range of study designs, different measuring end points and scales, difficulty

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quantifying and qualifying cough, different ages of children studied, small numbers of children studied such as the Paul report, different medications and dosage studies are some of the issues making quality systematic review difficult, but none of the above reviews found evidence supporting the effectiveness of medications in the treatment of cough and colds in children.

Health care providers, especially pediatric providers must always weigh the benefit risk profile of any medication recommended or prescribed to their children. The American Academy of Pediatrics long ago advised against the use of cough suppressants such as codeine and Dextramethorphan. In 2000 the FDA Administration recommended that phenylpropylamine, a commonly used medication in OTC cough and cold medications, be removed from the U.S. market due to its link to dangerous cardiovascular side effects.

And within the past year we have heard from the Center for Disease Control about the report of and warning of care-givers and clinicians of the

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risks for serious illness or fatal overdose from administration of cough and cold medications to children under the age of 2.

Although most of the concerns regarding hazards of medications have been focused on young children, the easy availability of OTC cough and

cold preparation and perceived safety may have also contributed to them being abused by older children.

In 2006, over-the-counter sales of cold medications containing pseudoephedrine were banned in hopes of curbing the elicit manufacture of methamphetamine. The antitussive Dextramethorphan has been associated with increasing abuse by school-aged children and adolescents due to the euphoric affect caused by high doses of this drug.

Healthy children have been found to cough 1 to 34 times a day. Interesting. Children, especially preschool-aged children and younger children have 5 to 8 colds each year with an average duration of cold symptoms lasting 7 to 10 days, with a cough often lingering for up to three weeks. Would we really want these children treated for that

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many cold symptom days.

Cough is an important reflex that protects and clears the airway. As health providers we need to educate parents and caretakers about the frequency and normalcy of cold symptoms, the efficacy and safety of medications used to try and relieve symptoms, non-pharmacological comfort measures to use in the home and signs and symptoms of illness warranting evaluation by health care providers.

Watchful waiting for the normal body defenses to restore health is an appropriate and safe management strategy for healthy children with a common cold.

Children with chronic health conditions, symptoms lasting longer than two weeks, progressing in severity or associated with additional signs and symptoms beyond the common cold should be evaluated by their health care provider and not treated at home with OTC medications.

Just last week I saw a four year old in the clinic with a known history of asthma. The

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mother had been treating -- had been trying to treat the child with cough medication, OTC cough medication for over a week, not recognizing cough as

a possible symptom of asthma.
The delay in appropriate treatment for the cough resulted in acute asthma episode.
So in summary, one, current research findings on efficacy and safety of cough and cold preparations do not support their use in children. Best practices guidelines and evidence-based practice principles should be followed in the management of cold symptoms in children.
Two, additional well-designed, randomized placebo controlled research in children of varying ages is necessary to further evaluate the efficacy of individual pharmacotherapy agents.
Three, current cough and cold preparations often combine drug ingredients increasing the risks of adverse reactions in children or the potential for overdosing when more than one OTC medication is administered to a child.
Four, watchful waiting for symptom

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resolution is an appropriate management plan when cough and cold symptoms are determined to be caused by the common cold.
And five, education of parents and caretakers on home management of cough and cold symptoms, symptoms warranting further evaluation and assessment by their health care provider. The lack of current research supporting the efficacy of pharmacotherapy for symptom management and OTC potential for adverse reactions or drug abuse should be the priority intervention of all health care providers.
I would ask if you're going to be labeling the medications that you use the word health care provider instead of doctor or physician so that we can include all the nurse practitioners who help care for the children of America.
Thank you.
MARY TINETTI: Thank you, I think with the size of the label we'll have to come up with a shorter term to cover all of us.
Next is Peter Lurie from the Public

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Citizen Health Research Group.

PETER LURIE: Just when I was about to make a joke -- right, about being tall, it turned out to be funnier than I thought.

All right. That should do. Thanks.

Good morning, I'm Peter Lurie, I'm Deputy Director of the Health Research Group of Public Citizen. I have no conflicts of interest to disclose. Public Citizen takes no money from either the Government or industry.

And I urge you to look closely at the conflicts of some of my prior speakers as well as some of the consultants who have presented to this meeting as well.

I'd like to rise to the challenge offered by Dr. Ganley's line of questioning about the 0 to 6 versus the 6 to 12 group of patients and I'd like to rise to that challenge by saying we think that products up until the age of 12 ought to be taken from the market or restricted. That's what the data require, that's what logic and the science show, that's what ought to happen.

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We also think that any formulation or drug delivery device such as a syringe or a dropper that makes it clear that they really are intended for children that are under the age of 2, certainly frankly under the age of 12, those should also not be permitted for sale.

As you've heard several times I'm sure in the last couple of days, there are two routes to approval of these products, one is through the so-called, the direct route and the other through the indirect route and the question asked of the gentlemen from the AAP was how do you, in effect, choose between them.

Well one certainly has to do with feasibility and it has to do with cost, I suppose, and also has to do with what we know about the extrapolatability, if that's a word, from children to -- or from adults to children. But in this case we should remember that what we have is a direct route that has been affirmatively proved to show

that these products do not work. So when you have negative direct evidence, it is not intelligent to

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take indirect evidence to somehow overcome that.

So the only way to overcome negative direct evidence is with positive direct evidence and it doesn't exist. So let me talk about those two routes to approval in turn.

First, the direct route of evidence. The FDA found 11 clinical trials, they've looked at this over a 50-year period of time, a remarkably small number, and frankly to say that there are 11 is an exaggeration in that numerous of these trials had no placebo groups, it's not clear if they were blinded, it's not clear if they were randomized, very, very poor studies, an enormous knowledge gap after a 500 million dollars a year in sales of these products.

The FDA concluded, and we agree that based on the review of published clinical trials, which is to say nothing of those that the industry has chosen not to publish, in children one and a half months to 18 years of age, there's no evidence, convincing evidence of effectiveness of the cough and cold medications when used to treat symptoms of

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the common cold in this population.

The AAP agreed as well, OTC cough and cold products constitute a group of products that do not produce any discernible health benefits in this population and they were referring to children under the age of 6. Similar comments from the American College of Chest Physicians.

Last night I went back and looked at these 11 clinical trials to see if there was any basis for this division at the age of 6. I can't find any. The studies are generally quite small. Not one of the studies reports sufficient data to make a distinction between the younger and older children and as long as there's no evidence of a difference, we have to assume that the conclusion of lack of efficacy that ensues from these studies applies to all of them.

So that takes care I think of the direct line, there's simply no evidence for that.

Now let's look at the indirect method of getting these products on the market, what's unfortunately been done and which we think is

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inappropriate. There are five steps that you would have to meet, five conditions that would have to be met and each and every one of these would have to be met.

The first criteria would be that the product would have to be effective in adults, but even that is not clear. The Cochran conducted a review of adult only cough and cold medications and concluded, quote, "Over-the-counter cough medicines cannot be recommended because there's no good evidence of their effectiveness," they were talking about adults only. Condition one in the indirect category not met.

Second category of information that would have to be met, there would have to be a reasonable biological basis to assume that either, that both the pharmacological responses and the disease processes were similar in adults and children.

The AAP, though, said extrapolation of therapeutic data from adults to children, although common, is fraught with danger, went on to note that

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in all four of the basic elements of pharmacokinetics, drug absorption, distribution, metabolism, elimination, that there are differences that occur during childhood development. So, condition number two, not met.

Condition number three, there would have to be adequate pharmacokinetic data in children and the very way in which these dosage recommendations have come to be put in place is frankly laughable.

How can we possibly have a series of recommendations that are the same regardless of the drug. I mean that's, that's simply not scientific. In advance of this hearing the FDA did conduct a pharmacological review of the products and concluded

that robust and well-designed clinical pharmacokinetic studies are currently lacking for cough and cold medications, they're referring to children.

Actually, if you look at the pharmacology review, you realize that to the extent there are any data, and there are very few, they confirm that there is no basis for assuming similar

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areas under the curve in adults and children and for the studies offered for pseudoephedrine, the AUC was 52 to 72 percent that of in adults and for Chlorpheniramine, the only other product for which there was any information, the AUC was 68 percent in children what it is in adults.

We are past these days of making guesses based on studies like this which are so very few and poorly conducted because we're now in the age of pediatric exclusivity in an age in which there are, in fact, lots of pediatric studies being done and we've learned that the assumption as stated that children are just small adults is just not based in realty. There are 25 products under the BPCA alone that have had to have dosing adjustments and in 28 cases the pediatric study proved that although the product worked in adults, it did not work in children.

So, condition number three that there would have to be pharmacokinetic data, not met.

Condition number four, the drugs would have to be reasonably safe for use in children.

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What we've heard about the 123 fatal cases that have been reported to the AER system, and we know that this is an underestimate in part because there's been no requirement for the manufacturer should they learn about an adverse event to even report it to the FDA, so with massive under-reporting for prescription drugs, we know it's still larger for over-the-counter drugs.

Moreover, despite the sponsor's desire to shift the blame to the parents of these patients who have overdosed, the fact is that the safety

review noted that some of these doses are, sorry, some of these adverse events and deaths have occurred at the usual doses, so it's not simply a question of overdose. So, condition number four, reasonably safe for use in children, not met.

Fifth condition that would have to be met, there would have to be possible -- to use this product in accordance with adequate labeling, but the division of medication errors and technical support at FDA mentioned all the things we've heard about, concurrent use of therapies containing the

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same active ingredients, therapies in the same therapeutic class, misinterpretation of directions, misuse of measuring devices, formulation changes and then the 800 of these products which we somehow have, despite there only being five or six active ingredients.

So, there are five criteria that would need to be met, all five in order to get to efficacy through the indirect route and not a single one of them has been met.

Instead what we hear is a lot about how the industry is willing to pull the products for those people willing to sign the statement under the age of 2. We hear about new pharmacokinetic studies, we hear about educational campaigns, educational campaigns which by the way are likely instead to turn to marketing campaigns, so I don't think that their solution to the problem marketing currently is to have in effect more marketing.

You cannot compensate for inefficacy by doing more pharmacokinetic studies, by educational campaigns or by labeling changes if the product does

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not work, and these products have not been shown to do so by either the direct or the indirect route, then it's time to cut bait and admit that it's time to remove these products as best as possible from the market.

Now of course you can't do that entirely because there are adults who use these products and we take no position at least in this hearing about

whether or not they actually work there, although as I've said, the Cochran review suggests that they do not.

So how do you restrict the availability of these products for children? Well there are five ways. First, the delivery devices that are intended only for children like droppers and syringes, chewable tablets, all of those should be removed from the market.

Second, the labels exultation against pediatric use should be extended to children 12 years and under because that's what the data demand.

Third, the labels should clearly state

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that there's no evidence of efficacy and that these products can be dangerous for these 12 and under age group. There should be no photographs, either representations of children on the boxes and finally, we recommend that only single ingredient formulations be sold.

That is -- and would encourage the rationale prescribing of these drugs or the use of these drugs to the extent that they should be used at all instead of the shotgun approach that we are currently allowing to take place by allowing all of these multiple ingredient formulations on the market.

I'd be happy to take any questions anybody might have.

Thank you.

MARY TINETTI: Thank you.

CHARLIE GANLEY: Can I ask a question real quick?

MARY TINETTI: Sure.

CHARLIE GANLEY: On your last statement about the combinations, the, you know, one of the

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viewers had recommended that it be cut off at 6, so is your recommendation to cut off at 6 or that there should be no combinations at all?

PETER LURIE: No, it extends to 12.

CHARLIE GANLEY: Even, I was talking

about for everyone, we're talking about children now, is that what you're --

PETER LURIE: Yes, talking about children through the age of 12.

CHARLIE GANLEY: Okay.

PETER LURIE: Everything that I say applies to all of it, because we don't see it, any basis for making that distinction.

CHARLIE GANLEY: Okay.

MARY TINETTI: Thank you. Dr. Parker wants to make sure we define today what is a child, that might be the most challenging part of this, particularly for those of us who have teen-agers.

Next is Daniel Mannello.

DANIEL MANNELLO: Hello. Good morning. My name is Dan Mannello and I'm here today to share with you not any type of clinical research or study

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but a real life scenario about my family that has been destroyed from the injection of Dimetapp when it contained pph.

I'm well aware this ingredient has since been removed and removed from the shelves and then they have the audacity to re-introduce this product that is now pph free, as if it was something special. Now they want to re-label this product again. This is absurd.

Being a single father just compounds the fact that I have two children, my 12-year-old daughter, Alexis, and my 9-year-old son, D.J. He's had seizures since he was 18 months old.

My son became ill with flu-like symptoms when he was only 8 weeks old at the time and his pediatric doctor advised us to simply give him Dimetapp. Due to his age he could not prescribe him any medication. This went on for approximately six months and every time we took my son to the doctor, it was the same reply, simply give him Dimetapp, due to his age, he cannot prescribe him any medication.

Several months later my son was taken by

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ambulance to the emergency room and was diagnosed to have seizures, not the flu. The fact of the matter

is my son was on a continuous dose of Dimetapp for most of the first year of his life which now he has scar tissues on his brain resulting from a bursted blood vessel and now also has dysplasia.

After seven years of tests, trial and errors with every anticonvulsant drug, we're now only left with the option of brain surgery, which probably won't rid him of the seizures, rather subject him to less medication and less frequent seizure episodes.

My family and I are not looking for sorrow or sympathy today. Whatever I say will not change the fact that my son has been robbed of his life. You can't even imagine what it feels like as a parent when I ask my son like every parent does, what do you want to be when you grow up and his response is an astronaut, daddy, I'd love to fly a spaceship, knowing wholeheartedly that this could never happen due to this disability caused by these pediatric drugs that have absolutely no proof they

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improve the symptoms of a child's illness.

My daughter, on the other hand, is a straight A student, I know she will succeed in life.

My son, on the other hand, could only wonder what could have been.

Please do the right thing and remove these drugs from the shelves immediately, regardless of the losses of the large pharmaceutical giants. I would not wish my true life experiences on anyone, my worst enemies.

Just to express my level of concern in regards to these medications, since my son has been diagnosed with seizures I have expended all my finances and not been able to hold a professional position of employment and have traveled from Miami, all Children's Hospital, to Wayne State University in Michigan and everywhere in between seeking an answer to an apparently unanswerable question, why.

I will do anything in my power to help my son lead a normal life at whatever it costs. I cannot financially afford to be here today. Instead of making my mortgage payment, which I'm currently

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behind on, I financed my trip here from Largo, Florida, to voice my opinion. This should show each and every one of you decision-makers how important this is to do the right thing and remove these drugs from the shelves immediately.

Furthermore, after sitting in this meeting yesterday, there is definitely a wealth of knowledge among all you physicians and doctors and everybody out there today and I was impressed with your reports, however just a simple fact that this special meeting was called should be evidence enough that there's plenty of unanswered questions, unanswered issues surrounding these OTC drugs than just some of the statements I heard yesterday while sitting here, few and, few and sparse results, limitations, not precise, not well-defined, symptoms not frequently measured, limited clinical information should lead you to believe these OTC drugs need to be removed, re-evaluated by today's standards and only after that, be re-introduced to the consumer and not a day before.

The Mannello family would like to thank

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you for your time, God bless each and every one of you and give you the strength to make the right decision.

MARY TINETTI: Thank you, Mr. Mannello.

That concludes the public hearing part, so we're actually going to take our break now for the next 15 minutes, I'll start around 25 to and we'll start the discussion and questions at that time.

(Short recess taken)

MARY TINETTI: If everyone would please take their seat, we'll re-convene and continue the meeting and we're now actually entering I think probably the most challenging part of the, of the meeting where we're going to actually discuss the questions posed to us by the FDA and provide some answers for them.

I just wanted to let you know that, how the process will, will happen is, is that I'll, I'll

read the questions, I think there will probably be some discussion about the questions, we find that we want to make sure that we are all in agreement on

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what the purpose of the question is and so once we've all agreed on what the question should be, then there will be some, some of the questions are merely for discussion and others will be yes or no votes.

For the, for the yes or no votes, we'll, we'll, after we've actually asked people sequentially if they have any other comments, that we'll call for a vote and I'll ask everyone who votes yes to raise their hand and each of the yes people voting yes will state for the record their full name and that she is voting yes or no and we'll do the same for those who are responding no and also for those who wish to abstain.

Okay. Yeah, I was, somebody already asked me that as well. And I do want to remind all the speakers and all the Committee members to please identify themselves for the record when they do speak and I was remiss in reminding you that yesterday and again today, so please do that and also make sure that you do speak directly into the mic.

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I want to make sure that Dr. Rappley has joined us.

LAURA MARCIA RAPPLEY: Yes, I'm here.

MARY TINETTI: Okay, thank you. I think Charlie -- Dr. Ganley has a comment.

CHARLIE GANLEY: Yeah, I just wanted to clarify one of the errors in the preamble here about what the process is and sort of explain people through it and we can explain as we go through the questions all, some of the things that we need.

There's a sentence in the second paragraph of the preamble, it says if a decision is reached to require new studies for these products, rule-making would be needed to re-categorize these ingredients to category three, need more information, sponsors would have the opportunity to

perform these studies.
That should actually read, what we do since this is a final rule, it would be categorized as generally not, it's not generally recognized as safe and effective. It would still give the companies an opportunity to conduct the trials.

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Let me just give you some examples, if you, whatever recommendations you make today, you know, we take back to FDA and then make some decisions. We still have to go through a rule-making process.
For example, in August we published a rule for sunscreens that provided for UVA testing and new labeling. It's a proposed rule. We've received several thousand comments already, most of them positive, some negative. We have to take those comments and then make a determination what our final decision is.
Another example, last year we published a rule-making on hydroquinone which is skin-bleaching agents because we had some concerns about safety, we were recommending that it no longer be permitted in the monograph. We received 600 comments electronically and I think 26 comments that are essentially saying that we were just, we're just wrong, okay. Most of them were against us taking that action.
And so there's part of the process, is

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your weighing in, we weigh in, we put out a rule-making. The public, other pediatricians get to weigh in and then we go to a final rule.
If new information comes in in the interim, we'll take that into consideration, okay.
One of the questions in here which is number three is the question is what, is there something we really do need to do right now, okay, which, you know, would sort of say more immediacy than a rule-making and so if you have questions about that, we can clarify.
MARY TINETTI: Thank you.
JOHN JENKINS: Dr. Tinetti, if I can

also maybe help the Committee by describing a little bit what we're looking for with the question, you and I spoke at the break, actually the questions are formulated in what we hoped as a very logical manner to walk you through the types of answers we're looking for. So the first question as we typically do when we bring products to the Committee is we ask you about efficacy, we then ask you about safety and then question number three is essentially how, when

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you put those together, what do you say about whether these products should be used in children in the different age groups.

We've heard a lot about extrapolation of efficacy and I wanted to make it very clear to everyone, efficacy is the only part of the evaluation of these drugs in children that we extrapolate. We don't extrapolate the dose, we don't extrapolate the safety, we don't extrapolate the risk/benefit equation, we only extrapolate the efficacy and it's codified in the most recent version of CREA, I'd just like to read it briefly what the most recent version of PREA says about extrapolation. It says, "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude," and the Secretary here refers essentially to FDA, "may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients such as pharmacokinetic

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studies."

So our first question really is related to, the bottom line is we're interested in your opinion on whether you can extrapolate efficacy from adults, from studies that are available in adults to children for the cough, cold uses of these products, we start out that question 1A with kind of a discussion question, we're very much aware and we presented to you that there are studies that have been conducted of these agents in children for these

indications and many of them have not demonstrated a positive finding.

We're interested in you discussing those first and how they relate to your thinking about whether you can extrapolate efficacy from adults to children. We've heard some people say these drugs don't work in children. What we really have presented is that the studies have not demonstrated in general that they work in children, that's different from saying they absolutely do not work in children. So we're interested in hearing your thoughts about the impact of the available data, on

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your thoughts about efficacy in children and then how that impacts on your recommendations for extrapolation. And be happy to have further discussions.

It's really key for us if you think that extrapolation is not appropriate for us to understand why you don't think extrapolation is appropriate in this case for efficacy because as you know and as we've discussed, many of these same ingredients are also marketed under the monograph and under approved new drug applications for treatment of allergic rhinitis, so if you don't think they can be extrapolated for cough, cold, we're going to have to go through the exercise of can we extrapolate for allergic rhinitis, which we do on a fairly routine basis.

I just wanted to give you very quickly an understanding of what are some of the indications where FDA has extrapolated efficacy from adults to children over the years and those include things such as seasonal allergic rhinitis, recurrent herpes labialis, allergic conjunctivitis, acute bacterial

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sinusitis, organ rejection, aphthous ulcers and complicated skin and skin structure infection. So those are places where we over the course of the last 15 years under the pediatric rule and PREA have determined that the disease is sufficiently similar to adults as it is to children to allow us to extrapolate information about efficacy, but again,

we have not extrapolated in those cases the dosing recommendations, the safety information and the risk benefits, so you could, you can conclude that extrapolation is acceptable, but that's not all that you need to get to an approval.

So, happy to take any other questions about that but we're really interested in the Committee's views on extrapolation for cough, cold and if you feel that you can't extrapolate, we really need a clear understanding of why you don't think we can extrapolate in this case.

MARY TINETTI: Can you identify yourself?

RALPH D'AGOSTINO: Ralph D'Agostino.

Charlie, when you were going over the

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preamble, did you say in, you're replacing the category 3 here with category 2, did you say that or did I misunderstand?

CHARLIE GANLEY: Yeah, that's correct. If there's a final monograph, the --

RALPH D'AGOSTINO: Oh, by the time the final comes, it has to be either 1 or 2.

CHARLIE GANLEY: No, the proposal, when there's a final monograph, which there are now for all the various categories of drugs that fit under cough and cold, when there's a final monograph, if we go back to amend it and are seeking new data, we'd have to characterize it as being category 2.

Now in this case if that was the case that we, you know, if we were going down that path, we can say that it's category 2 for, you know, children less than 12, that would not affect adult products, per se.

RALPH D'AGOSTINO: Exactly, okay, that's my question, yeah. So there's no implication on outside of the children.

CHARLIE GANLEY: No.

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RALPH D'AGOSTINO: Thank you.

MARY TINETTI: Dr. Joad.

JESSE JOAD: Yeah, before we start, I've been concerned --

MARY TINETTI: Just identify yourself.
JESSE JOAD: I'm sorry, I'm Jesse Joad. I've been concerned that you've been saying cough and cold and cough is cough, cough could be chronic cough, it could be a lot of things and a cough is part of a cold, so I'm assuming you, when you say cough and cold you mean cough as part of a cold and a cold.
CHARLIE GANLEY: Well, no, I probably, you know, it's sort of thrown under that category where that Committee got together and the Committee was the Cold, Cough Bronchodilators Committee. But each of these drugs have different indications.
JESSE JOAD: Exactly, but I hope we're not talking about cough in children because that's really a big subject that we haven't even touched on here. I mean there's lots of reasons for cough in children that have nothing to do with a cold and

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hopefully we're not talking about that.
MARY TINETTI: Did you want to propose, Dr. Joad, some limits on what we're going to discuss, because that certainly will help our discussion, I think that's come up a couple of times, what's the scope of --
JESSE JOAD: Yeah, I would just say a cold, because a cold includes -- can include a cough, it can include a stuffy nose, but having cough as a separate word in there I think is very confusing.
CHARLIE GANLEY: Yeah, I'll have to get you the exact indication that is listed in the monograph and that may help clarify it or confuse it for you, but I'll have, I'll try to get the exact language here, so.
MARY TINETTI: Okay. Dr. Gorman had -- is this more clarification points? Did you --
RICHARD GORMAN: This is Dr. Gorman, it was to answer the question about extrapolation. I can wait for clarifications to finish.
MARY TINETTI: These, any questions

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concerning clarification of our scope?

Dr. Calhoun.
WILLIAM CALHOUN: For Dr. Jenkins, could you clarify for me --
MARY TINETTI: Can you identify yourself?
WILLIAM CALHOUN: I'm sorry, Bill Calhoun, could you clarify for me the Agency's position on extrapolation with respect to the comparability of adults and kids, does the Agency, is the Agency's position that you need affirmative evidence that the pathophysiology and responses are similar in order for extrapolation to be appropriate or is it the Agency's position that you need affirmative evidence that the two are different in some regard for extrapolation not to be appropriate?
JOHN JENKINS: Clearly this is an area where judgment has to come into play and one of the slide presentations yesterday, Dr. Roy actually presented the algorithm we follow, it's on slide 24 of Dr. Roy's slide set yesterday and it follows what I read you earlier from the PREA statement. It says
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the Secretary may conclude that pediatric effectiveness can be extrapolated. It doesn't say must, it says may and you'll see in his slides it says that if there's reasonable, if it's reasonable to assume that the similar disease progression, similar response to intervention, then you go down the pathway to the right and where you can say reasonable, assume similar concentration response in pediatric and adults, if you say yes or no.
So, those are the criteria we applied. It requires judgment on deciding what you think you can extrapolate or not and we don't extrapolate in all cases. I read you some of the indications where we have extrapolated. Indications where we haven't extrapolated include things like depression in children, seizure disorders in children, hypertension, areas where people have not been comfortable making that assumption based on all of the available scientific evidence that the disease progression and the response to intervention is likely to be similar. We don't require that there

be absolute concrete scientific evidence that they
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are, quote, similar. We look at all the available information to make that determination.

I think -- I'd also like to ask Dr. Nelson who has joined us again this morning from our office of pediatric therapeutics to comment a bit on some of the ethical issues that come up in pediatric research, because I think that's something we need to be aware of and you need to be aware of as well because conducting clinical trials in adults and conducting clinical trials in children is a very different enterprise and there are very different ethical issues that come up.

So, Skip, do you want to speak to that some.

SKIP NELSON: Thanks, John, just before I do, let me just make the additional point that extrapolation has to be also --

MARY TINETTI: Dr. Nelson, could you just identify yourself.

SKIP NELSON: Dr. Nelson, sorry, Office of Pediatric Therapeutics and I apologize for being late, I had another talk I had to give at 8 this
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morning about extrapolation from animal data which -- the only other point to add to extrapolation before commenting on the ethics is the fact that it needs to be placed within a developmental context, meaning that you could conclude you can extrapolate to, say, a teen-ager but not extrapolate to a toddler.

You know, so I mean it's not, it's not just adults to children, but it's working your way all the way down through the physiology that is changing, so that judgment has to be applied across a range of developmental perspectives and pretty much depends upon the disease category and what you might anticipate in terms of path of physiology.

In terms of the ethics, the only point I would make is that it, the reason of extrapolation I think is a very important principle, is that the starting point for pediatric research is that you

should never subject a child to the risks of research unless it's to answer a scientific question that is essential to the health and well-being of that child and cannot be answered in any other way.

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So basically if you could use an adult to answer a question that then is pertinent to the child, you should do that.

So extrapolation is sort of a scientific application, if you will, or the specification of that principle which judgment then needs to apply as to whether or not you can or you cannot do that and you've already heard conditions where you can and conditions where you can't. The basic idea is if you can take data that's available in adults and use it for pediatrics, you should, but then you need to supplement it where you need to and I think that's really pretty much the foundation for the pediatric drug development program.

MARY TINETTI: Okay, thank you. Dr. Taylor.

ROBERT TAYLOR: On this issue of extrapolation and looking at --

MARY TINETTI: Dr. Taylor, could you identify yourself.

ROBERT TAYLOR: Robert Taylor. Could you put the slide back up on extrapolation that,

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from Dr. Roy's talk just a moment ago, because I'm a bit confused about the decision-tree for extrapolation. And the issue is you can extrapolate when the disease process is similar, but these drugs don't treat the disease. These drugs treat the symptoms.

So how do you reconcile that in this decision-tree?

JOHN JENKINS: You base your decision on the indication that the drugs are seeking. So here the drugs are symptomatic relief of the symptoms associated with the cold or with a cough, so you're looking at, you know, in the common cold do you think that the disease progression is generally similar in adults as it is to children, do children

tend to have the same symptoms, are they, are they likely based on the same pathophysiology, et cetera. So you don't focus -- again, you're not focusing here on do these drugs treat the common cold, they don't cure the viral infection, you're treating the symptoms.

So that's how we generally do our

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thought exercise for drugs, is we're always looking at the indication. Our statute is even based on the intended use, so all of our statutory provisions are based on, for example, safe and effective for the intended use when used according to the labeling. So it's always the intended use which here would be the symptomatic relief of the condition -- of the symptoms associated with the common cold.

ROBERT TAYLOR: But that's a little bit different from the other examples you use, like hypertension in which that's a clear disease process, those are not symptoms that you're treating with those drugs, so I'm just saying that there's a little bit of a disconnect between symptoms and the decision-tree that you have here about --

JOHN JENKINS: Well a better analogy for the common cold than hypertension might be allergic rhinitis. You know, these same drugs are used to treat the symptoms of allergic rhinitis. They don't mitigate the allergic rhinitis process, per se, they're, they're treating the symptoms, so we go down this same decision-tree, do we think allergic

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rhinitis in adults is sufficiently similar to allergic rhinitis in children that would allow us to extrapolated demonstrated benefit in adults to children.

So it's really, again, based on what the drugs are intending to treat, and hypertension you're looking at the blood pressure. We, obviously, have concluded that, you know, the causes of hypertension in children may be very different than the causes of hypertension in adults which may lead you to question whether you can extrapolate the efficacy, for example, of an ace inhibitor from

adults to children where the pathophysiology could be quite different.

ROBERT TAYLOR: I guess my point is that in many cases in your prior examples, like hypertension, you're really looking at a proximal integrated entity related to the disease where the symptom is really more distal to the disease process.

MARY TINETTI: Can we just perhaps clarify that for our purposes, our question is is

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there a similar clinical manifestation in terms of symptoms and is there a similar physiology and anatomy that are leading to those symptoms, would you be comfortable with that and forgot the sort of disease progression, would you be comfortable with that?

ROBERT TAYLOR: Yes.

MARY TINETTI: Okay, thanks.

Dr. Daum.

ROBERT DAUM: So I need some clarification.

MARY TINETTI: Please identify yourself.

ROBERT DAUM: Oh, I apologize, I was thinking I'm going to identify myself, I know I am and then --

MARY TINETTI: The first one who does identify themselves gets the prize.

ROBERT DAUM: Maybe if you called on us and didn't say our name it would be good, I don't know.

So, I need to know whether this is a theoretical or real extrapolation request, in other

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words, would the FDA in their comments, Dr. Jenkins in particular, like us to assume that there exists a body of data unseen at this meeting in adults of each one of these ingredients that we're talking about, the eight drugs or however many there are, individually tested and prospective randomized studies in adults and that there's a solid efficacy base there, then the question is can we take from that database, which I haven't seen at this meeting,

but I'm sure exists from the way people are commenting, and extrapolate back to kids. That's the question. It's a theoretical question.

And then I guess the separate thing that we could do as a Committee, although I'm not sure we're properly armed to do it, is to parse the adult data and look and see what we believe about how good they are and then look at the extrapolation issue after we decide about that.

So I'd like to, is this a virtual extrapolation request or is this an -- the data exists and we just haven't reviewed them but we all know they're there except me?

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JOHN JENKINS: John Jenkins, again from FDA. Let me point first back to the language I read from the most recent version of PREA, which was just signed into law by the President last month and the key word I want to emphasize, it says, "The Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults," so the purest application of this extrapolation is one where we apply it prospectively where, you know, normally drug development proceeds first in adults and then makes its way towards children for lots of reasons, so the purest example is we have a new drug, it's never been approved in the United States before, they have adequate and well-controlled studies to demonstrate that it's safe and effective in adults and then we extrapolate that finding of effectiveness to children and decide that instead of having to do efficacy studies, they can, we can select the dose based on pk, safety information in children and an assessment of the risk/benefit.

The drugs you're talking about today are

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the monograph drugs which they're in the monograph because they're old drugs, they were in the marketplace before 1972 when the monograph process was started, so the level of evidence is going to be different, but recognize that the monograph review process applied those same standards for

determining, you know, safe and effective.

So in the monograph process these were determined to be effective through looking at the available data. Are the data as good as you might get prospectively on the new drug or adequate and well-controlled studies; probably not, but you do need to factor in your extrapolation comfort with your comfort for the effect in adults. We haven't presented that to you today or yesterday, with the session, for example, Dr. Starke yesterday in his presentation did show you an example for clemastine or Tavist which was approved for use in the common cold in 1996 and he showed you the, an example of the type of adequate and well-controlled study that was done to demonstrate the effect of Tavist in children 12 and above and adults and you may want to

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refer back to that study design and the results.

We know from long experience that the effect size of antihistamines, decongestants, cough suppressants in these symptomatic conditions is often relatively small on an average population basis, so one of the things we've learned and the companies have learned is you have to have fairly large studies to account for all the variability, the natural progression of the disease, which is that it tends to get better to be able to show statistically that these are better.

So, for example, the Tavist study had 200 people per ARM, so you need to factor that in as you're looking at some of the pediatric studies that were presented, how large were they, were they adequately powered, et cetera.

So, you have to look at the information you have in adults and your comfort level that you've demonstrated effectiveness in adults and then your willingness to extrapolate that to children.

MARY TINETTI: Dr. Daum.

ROBERT DAUM: I'm sorry, I have one

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follow up. So I'm still not quite clear on which of the pathways, at least in my mind there's at least two you would like us to follow.

The first one is to assume that the adult data are there and solid and so your only question is will we be willing to sort of import them into pediatric use, extrapolate.

The second question is are the adult data not there and, or shaky or incomplete and then on that basis, could we then bring, extrapolate them into children and which data would we extrapolate and which ones we wouldn't. It's a much more specific task --

MARY TINETTI: Let me cut to the quick because I think we haven't really heard very much of the adult data, but I think in our package, basically, we could all agree that there are data in adults, it's modest, at best. It probably -- it certainly is not at the level of new drugs, but there is some modest evidence in favor of effectiveness, particularly with the, with the decongestants.

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And I think unless people want to add anything else, that's really the state of the evidence in adults that we are asked to extrapolate. Would you agree? Dr. Starke here?

JOHN JENKINS: John Jenkins, if I could follow up on that, keep in mind that the monograph process went through the expert panels and as Dr. Chang showed you yesterday, about a third of the products that were in the marketplace before the panel review survived through the monograph to the final monograph, so there was a process by which all of the available evidence was reviewed both by the panels and then by the FDA and then through a rule-making process we got to the point of saying that these products have been demonstrated to be safe and effective in adults.

And the real question from the monograph was we extrapolated that finding from adults to children, which is similar to what you're being asked here.

MARY TINETTI: I think we understand that point, so I guess is there any other further

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discussion, do we want any further discussion on the adult data or can we just be willing to accept there's some data, it was sufficient to pass the monograph, it's modest, at best.

Dr. D'Agostino.

RALPH D'AGOSTINO: Ralph D'Agostino, I want the prize.

I, actually, was involved with a lot of the review process on the, or part of the process with the monograph and the data is, there are lots of bad studies and one had to be very clever in terms of extracting from the studies, was there really a solid basis and then the company's responses did get more responsive, not that they weren't responsive, but understood what a cold should be, that you can't recruit people who have a cold for seven days and expect to find an affect within three days and there were quite bit of things done.

I mean I think it's safe to say and correct to say that there is a data set that supports the adults and one can say we should have

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seen it here, but I think the data is there and it's not all trivial and some of the, certainly the later things that came on were very solid studies, the 1995 presentation, for example, that was a really solid study.

So I think we have the comfort of saying the adult data is there and it's -- the issue I think is can you extrapolate to children is, and what's, presentations here have proven a lot of confusion, to me anyway, and I'd be very interested in hearing what the expert, when we get to what the experts are going to be able to say about this extrapolation.

MARY TINETTI: Okay, and so --

ROBERT DAUM: Can I just ask him one quick follow up?

MARY TINETTI: Real quick, very quick.

ROBERT DAUM: Robert Daum, Chicago. When you say the adult data are there, do you mean for all eight drugs we're talking about, all

14 drugs we're talking about?
RALPH D'AGOSTINO: No, that's a good
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question, they were in terms of the ingredients, I did the meta analysis where we lumped together a number of the antihistamines and so forth but what we looked at, was there, was there as a class of drugs for a generation antihistamines, was there a class affect going on and then we looked at individual, we looked at individual ingredients and found that that was very consistent.
I do not have an answer to has every single drug been looked at in every single combination, I obviously don't have an answer to that, but there was quite a rigorous activity going on where of classes and then individual drugs were examined.
MARY TINETTI: Dr. Parker.
RUTH PARKER: This is just a request to consider in our responses, if it would be useful to the FDA as we respond to the questions to try to provide useful information, when we see the words, and I've been confused since the, since the petition was presented about this, when we see cough and cold, I'm wondering if we could say cough and cold
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for the common cold or for bad cold, because I, I think, you know, when you consider the role of the consumer in self-diagnosing to purchase over the counter, you have to really try to think of what, you know, what the average consumer is thinking when they purchase it.
And, you know, this tease around whether or not it came from having seasonal allergies, allergic rhinitis, whatever it is, versus a common cold or a bad cold is a point of confusion.
So for me, if I add that, cough, cold products for the common cold, I am more able to answer it with clarity than I am if it's just cough which could be from any number of things or cold which also I think could probably be interpreted. So that's a point question, cough, cold for the common cold or a bad cold.

CHARLIE GANLEY: Yeah, I'm going, we're in the process of putting some slides together that goes through each category and what the claims would be and I think Joad, Dr. Joad raised a good point is that there is a claim for just cough and it doesn't

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have anything associated -- you can have a claim cough for the common cold or bronchio irritants, but you can also have a temporary relieves cough, for example, that's non-specific, okay.

So --

MARY TINETTI: I think the question was so -- Charlie, can we specify what we're addressing today, is that your question, Dr. Parker?

CHARLIE GANLEY: Yes, if you want to limit it to the common cold, and that's what the petitioner had requested.

MARY TINETTI: Okay, so maybe we can add those words to make it clear so we know.

RUTH PARKER: That's good.

MARY TINETTI: Okay, thank you.

RUTH PARKER: And then the other point of clarity for me would be, and I know this is going to come up in most questions and extrapolation on down the line would be, and I pose it as a specific which will open it up to discussion I'm sure, but I'm back to the what is a child and in my reading of these, because younger children, adult, I mean these

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words come up, so I am, imposing that a, that this may be children are 12 and under, younger child's under 2, then you say where is an adult and anybody who has a 13 year old has to ask what that means, but in terms of useful information, I think if we don't clarify what an adult is and what a child is and what a younger child is with numbers, it's, it's going to be less useful information.

So I ask that before we get into specific questions, because those terms are used repeatedly, as the mother of four.

JOHN JENKINS: John Jenkins, let me, historically many of the trials of these ingredients in adults for allergic rhinitis or cold, whatever,

have included -- enrolled patients 12 years of age and older. I can't say that that's in every trial or for every drug, but most of the time when we see studies in this area, they include 12 and above because 12 and above are generally in the age range where people can fill out the diaries and do the symptom scores and be reliable in reporting that type of information.

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So you may want to consider 12 and above and 12 and below as just kind of a historical cut point of how the trials have generally been done.

MARY TINETTI: Thank you.

Dr. Rosenthal.

JEFF ROSENTHAL: Jeff Rosenthal, I have two questions, two points I'd like to clarify. One is is it the Agency's position that, that this process of extrapolation is reasonable only in the absence of pediatric specific data or is it, does the Agency consider it a reasonable process to engage in even if there is pediatric data? That's the first question.

And the second is I actually thought it was very interesting, Dr. Nelson's comment regarding the use of extrapolation to protect kids from the risks of studies and I can understand that reasoning in, in the prospective context, but I'm wondering about its application in the retrospective context, I'm wondering if I can get some clarification on, on where the Agency stands on these points.

JOHN JENKINS: Yeah, John Jenkins, I'll

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start and then ask Dr. Nelson to comment on the second part.

As I said, the purest form of this extrapolation is what I described earlier, where you have adult data, you don't yet have much, if any, data in children and you make a judgment on whether you think it's reasonable to extrapolate the efficacy. And if the answer is yes, then that drives what we ask for for the rest of the program. We would then ask for pharmacokinetic data in various age groups to get the right dose, to match

the adult exposure.

We often ask for safety studies in children to collect adverse event information to see if the adverse event profile is similar to what we see in adults and then obviously we have to make a risk/benefit calculation for each of those age groups.

The complexity that you're getting to for this situation is that there are existing studies, you heard about them yesterday, of some of these agents in the pediatric population. Many of

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them did not demonstrate efficacy to a statistical level that we would normally expect and that's why we have question 1A where we want you to discuss, you know, the relevance of those data and how it impacts on your thinking. For example, we've heard some say these studies were negative, therefore, these drugs don't work.

Is that the Committee's view or is it more the Committee's view that the studies haven't demonstrated the benefit but maybe for various reasons that you could point to, sample size, end points, et cetera, we can understand why maybe those studies didn't work and we still think that extrapolation makes sense.

So that's, you're putting the nail right on the right place where there are existing data here. This is not the clean situation. There are existing data.

MARY TINETTI: So can I just summarize, if there were data in children that were effective, obviously it would be a moot point.

JOHN JENKINS: Right.

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MARY TINETTI: We're in a situation where there are data that are not effective, so can we extrapolate, I think is that a fair, is that, is that a fair summary?

JOHN JENKINS: There are existing data. They're mixed. I think there were a few studies that were considered positive but you'll have to assess whether you think those studies were really

adequate.
MARY TINETTI: But in terms of the point of extrapolation.
Okay.
JOHN JENKINS: Dr. Nelson may want to talk about the ethical issues.
MARY TINETTI: Dr. Nelson.
SKIP NELSON: I guess in commenting on the retrospective, prospective issue, I mean you're being asked to address what should be done going forward in light of the full information around the data that exists as John went through, so this is a prospective application of a paradigm of pediatric drug development which to date has been worked on in
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the new drug application process and has been used less frequently in the OTC area.
So, I'm not sure I would say it's entirely a retrospective one, it just means that you've got a little bit more on the table in terms of data and history that you need to take into consideration than might exist in a situation where it was a new drug or a new chemical entity proposal.
JEFF ROSENTHAL: Jeff Rosenthal, if I can just sort of clarify this point, so I think if we're, if we're saying that, that -- let me see the best way to articulate this, so I mean I guess if, if we're using the drugs and saying that the drugs are effective and safe, then we're saying that the risk of use in kids is very low and it's not clear to me then that the risks of enrolling children in studies of these drugs is going to be anything but negligible and in that case does extrapolation still make sense?
SKIP NELSON: I guess my comments about the use of extrapolation does not necessarily imply that if you chose to do an active equivalent trial
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of two antihistamines it would be unethical, so, I think it's a much different point.
MARY TINETTI: Maybe a few more questions, then we can actually get to the questions because a lot of these things will probably come out

as we speak. So Dr. Newman and then Dr. D'Agostino and then we'll actually start on the questions.

TOM NEWMAN: Tom Newman, but maybe I'm out of order because I was, I guess I was going to address a question that Dr. Jenkins asked the Committee, but it's sort of an answer to this, so should I wait or just plow ahead?

MARY TINETTI: I'm not sure what you're saying, why don't you go ahead.

TOM NEWMAN: Okay, well I guess I think in terms of whether or not we can extrapolate, in this case the data that we have heard make it I think very hard to make the case that these drugs are generally --

MARY TINETTI: I'm sorry, if it is addressing the question of extrapolation, we will be getting to that, is that --

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TOM NEWMAN: Okay, yeah, I'm addressing these questions, so should I wait?

MARY TINETTI: Yeah, we'll be getting to that.

Dr. D'Agostino.

RALPH D'AGOSTINO: Ralph D'Agostino, just a brief comment about the -- or a question about the ethical issues, I mean we have a set of conditions that live number of parents think is perfectly fine and enthusiastically use the drugs, so people are using the drugs.

To put a study together that involves these, certainly a non-inferiority type of study would have ethical support, but even a placebo control that's a self-limiting condition, I mean do you see that there's insurmountable ethical issues with putting this study together here?

JOHN JENKINS: No, no, just let me comment, I don't think you could do a non-inferiority design because I don't know how you would interpret a non-inferiority design.

RALPH D'AGOSTINO: No, I wasn't saying

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we should, I think a placebo controlled study, but in terms of what's ethical here, there are a whole

degree of ethical studies I think with these drugs.
JOHN JENKINS: Right, you could clearly do a placebo controlled trial, you could do an active comparator where you're trying to show that you're better. I think it would be very hard to interpret an active comparator non-inferiority trial.
RALPH D'AGOSTINO: Yeah, well, erase that comment, it was just, I was just raising the ethical issues. There are many designs that I think could be done here.
MARY TINETTI: All right. Thank you.
Dr. Rappley, do you have any questions of clarification before we start on the questions?
LAURA MARCIA RAPPLEY: Well my comment relates to what you said earlier, Dr. Tinetti, and that is I think the question is is it permissible to extrapolate from mixed results in adults to children. Does the mixed result that we currently understand in adults then require a higher level of

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vigilance around the use of these meds in children that would lead us to ask for efficacy studies.
MARY TINETTI: Okay, thank you.
We'll actually start on the questions now.
So our first set of questions relate to efficacy. Is there evidence that these drugs do what they're intended to do. So the wording of the first question which will actually just be I think primarily a discussion but I think I will propose that we do a yes, no, at the end because I think it will help us as we progress, it's to discuss the available published studies and how they inform our knowledge regarding the efficacy of the monograph cold products for the common cold which we've now added in children under 12.
So I think, I mean I think essentially what this is getting at, is there sufficient data and is the data good enough to say either these drugs are effective or these drugs are not effective in children. So I'd perhaps have a general discussion about the, the quality of these studies

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and whether they informed efficacy, because I think that will be important as we go on to the subsequent questions.

Dr. D'Agostino.

RALPH D'AGOSTINO: Ralph D'Agostino. I mean the answer to me is quite clearly no. There are -- there have been studies, they haven't been able to show an effect. I would extend the comments and say I think it's probably because they're underpowered studies and poor designs for children, but there is not, I believe there is not a database for showing effectiveness in children.

MARY TINETTI: What about ineffectiveness?

RALPH D'AGOSTINO: I do not think that the studies can be interpreted that the drugs are ineffective. I think, as I say, they're mainly underpowered and probably inappropriate designs.

MARY TINETTI: Thank you.

Dr. Dure.

LEON DURE: Leon Dure, Birmingham.

Yes, I think I -- in going -- the prior

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discussion regarding the extrapolation issue, I mean I think that to summarize how I feel about this, I feel I'm in a state of true clinical equipoise because of the fact that the studies are described as insufficient and poor and I think somebody, Dr. Calhoun, made this statement yesterday about lack of effect. It's not, I don't remember what the other part of that was, but I don't think the problem here is that we think the studies are terrible or -- we think that the studies show a lack of effect, I think we think the studies are just insufficient to answer the question.

And so this, I'm a little mystified about the issue of ethics because I think that is the point about clinical equipoise, is this is the perfect time to do a clinical trial is when we really don't know the answer.

So I would say in answer to this question that they, there is not sufficient efficacy

data at all.
MARY TINETTI: Thank you.
Dr. Cnaan.

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AVITAL CNAAN: Avital Cnaan, I agree with Dr. D'Agostino that the studies do not support efficacy, however they don't show lack of efficacies, yes, because they're too small, but also primarily because we don't know what the right doses are in the absence of pk studies, so they --
MARY TINETTI: Pk, those studies are separate. This is purely effectiveness, we'll be getting to those.
AVITAL CNAAN: I understand that, however that means that these six studies that we have seen so many times over the past two days were possibly done at the incorrect doses to begin with, taking away from their value.
In addition, there was the main point of the measurement of outcome that was very long after when the expected effect was there.
So, there are a lot of other smaller limitations but there were enough limitations in these studies that what they can serve as is pilot studies for future studies, but are completely inconclusive at this time either way.

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MARY TINETTI: Thank you.
So I think so far we've heard that it's insufficient to say whether they were effective or ineffective for small sample size, inappropriate in outcomes and timing of those outcomes and dosing.
So are there any other comments in addition to that?
Dr. Hennessy.
SEAN HENNESSY: Sean Hennessy, the way we work in science is that we assume lack of effectiveness unless it's demonstrated and the studies that have been produced, while they don't conclusively prove lack of effect, you can never prove lack of effect. They suggest lack of effect.
They also demonstrate a higher rate of side effects in the active treatment group, so while

I don't think these studies preclude the conduct of future randomized trials to demonstrate the effectiveness, the data that we have now is that they don't seem to work and I'm wondering whether we can extrapolate that apparent lack of efficacy to adults.

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MARY TINETTI: That's the next Committee meeting and you'll chair it, thank you.

(Laughter).

Dr. Newman.

TOM NEWMAN: Tom Newman, I think that the, in order, in terms of coming to a decision on this and phrasing this, this is, the question is phrased discuss, but we might be able to take a shortcut if we phrase a yes or no question, is there, are these generally recognized as effective in children 2 to 12, meaning it's not just that we haven't proven that they're ineffective, but can we say that they're generally recognized as effective.

I would say the answer is no, that we've heard overwhelming evidence that they are at least not generally recognized as effective.

When hearing the questions about well should we do 2 to 6 or 6 to 12, what I heard pretty much when the petitioners and others were asked why not 6 to 12, the answer was sort of like well that was a political decision.

It doesn't seem like there was a firm

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scientific basis to divide at age 6, so I would just suggest that we, we phrase this 1A as the question are these generally recognized as effective when used as directed at age 2 to 12 and I would say the answer is no and that might make the discussion quicker.

MARY TINETTI: So you're saying I think we were actually going to change efficacy to in children less than 12. Would you --

TOM NEWMAN: Children less than 12 and I think if we say, not that we have to prove lack of effectiveness, but we just have to say that we can't say that they were generally recognized as

effective --
MARY TINETTI: I understand, right, I understand, we're not getting to that point, but I think we had clarified it was going to be for the common cold in children less than 12, are you comfortable with that as the first question?
TOM NEWMAN: Yes.
MARY TINETTI: Okay, thank you.
TOM NEWMAN: When used as directed.

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MARY TINETTI: When used as directed, thank you.
Dr. Gorman.
RICHARD GORMAN: Richard Gorman and I'm speaking on behalf of the professional health care organizations, but the analogies will be strictly my own, occasionally accused of colorful analogies.
I was very surprised by the questions from the Agency about a change in position from health care organizations on extrapolation.
For 30 years we've been in a rough and tumble and all the sharp edges have been worn off the stone. There has been no retreat or change in our position about extrapolation from adult data to --
MARY TINETTI: Dr. Gorman, we're not at extrapolation yet, can you hold that comment, we're just purely talking about efficacy right now in the studies that have been done in children.
RICHARD GORMAN: This is just leading into the efficacy question, if you allow me --
MARY TINETTI: Okay, if you get to the

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efficacy.
RICHARD GORMAN: Right. So the question became that in this particular case, we continued to hold as a default position, as a position we're very comfortable with, but the data about efficacy which is what we're talking about has been shown through BPCA that we're wrong on a particular number of times when we extrapolate efficacy from adult to children and we have become more sensitive to that signal so that when we see data, you can start to

use the statistical poo-poo that we do when we don't like the studies, that they don't give us the results that we want.

And I was in the poison control center movement when the original data about the efficacy about ipecac started to come up and something I'd been recommending for 30 years was called into question.

So, the data that we've seen show no efficacy and the Academy is comfortable with that particular thing, that we feel comfortable recommending to the Agency that efficacy cannot be

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extrapolated in this position and that efficacy studies would be required.

MARY TINETTI: Okay, thank you.

I think that's a good discussion. I guess my question to the FDA, is this sufficient, you don't pose us right now a yes, no question for number 1. I think the overall, overwhelming sentiment is that, that the existing studies are insufficient to address the question of efficacy for the common cold in children less than 12 and used for the indicated, as indicated.

Do you want a, any, us to pose a yes/no or is this sufficient for you as we move on to the second part of the question?

JOHN JENKINS: You have a yes/no in B and I think that's where we'd like to hear the yes/no. I would like to throw out if anyone wants to take it for discussion what happens in the situation where we don't have any data in children for the common cold, are we comfortable extrapolating where we don't have any data versus situations where we have some data from what may be

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inadequate studies and we say pointing to those, those make us uncomfortable so we have to have data, but in the absence of data would we say the same thing?

MARY TINETTI: I, I guess I'd rather us stay focused on our topic here at hand. I think that's a good question, but it may be beyond our

scope here today.
Dr. Daum.
ROBERT DAUM: So I'd like to suggest a rephrase of the way you summarized our discussion, if you would consider it, and you said that, I think you said that the studies in children are insufficient to judge whether these drugs are efficacious or not and I would like to rephrase it by saying the studies that are available do not demonstrate efficacy. They have limitations, they are few in number, they are underpowered, I mean all the things we've talked about, we'd like to see more studies done, more data, but the central conclusion is that they do not demonstrate efficacy.
MARY TINETTI: Fair enough. Any

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discussion on that point?
Dr. Newman.
TOM NEWMAN: Yeah, I guess I just disagree a little teeny bit with my statistical colleagues about whether the reason why they failed to show benefit is because they're underpowered. I think the available studies suggest that the drugs don't have any efficacy. It's not just that they, they fail to show efficacy, they suggest lack of efficacy.
And the point would be, yes, if you have a big enough study, you can eventually find probably some statistically significant benefit, but if your study is too large, you end up finding results which are statistically significant but not clinically significant and I think that's the case with some of the studies with adults where you have, it takes 200 people to show a difference between the groups and the magnitude of the difference in one of these studies, it was two sneezes a day, that was the difference, two sneezes a day and it was statistically significant.

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And so we, we don't want the studies to be too big and we want our standard to be not just a non-zero effect, but a clinically significant effect that would warrant families buying these medications

and subjecting the children to the admittedly small risk that they pose.

MARY TINETTI: So I think that was very much Dr. Daum's point, is that the existing data do not suggest effectiveness.

ROBERT DAUM: But he embellished it nicely, because it's not -- if the effect were, you know, 50 percent versus zero, the number of subjects studies might have been sufficient and what he's saying is that we have to take the conclusion of no efficacy with the power that they had to study it and it's a separate question of what power would we like, do we care whether three sneezes a day goes to two and then that's going to be a very big study.

So it's not clear that just expanding the power will solve the problem. I think that's Dr. Newman's point and it's very important.

MARY TINETTI: Fair enough. Are there

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any new points?

Dr. Cnaan.

AVITAL CNAAN: I would just like to say that I heard neither statistician say that the reason that there was no benefit is because they are underpowered. The studies are underpowered, the reason that they didn't show benefit may be because there is no benefit, we just don't know.

MARY TINETTI: We understand.

Yes, Dr. D'Agostino.

RALPH D'AGOSTINO: In the adults there are studies that have shown that the symptom was reduced by 50 percent which wasn't two sneezes a day. You pick a study that was maybe problematic or something and was large and showed an effect.

But I think, you know, these studies, if we get to talking about clinical trials, you're going to be talking of the order of magnitude of 400 to, 400 subjects studies, 200 in each group. OTC products oftentimes don't have huge effects, there will be a 58 percent change or something like that. This is your 40 percent placebo, 55 percent effect

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with the drug and so forth.

You can, you can take the task to get rid of all OTC drugs because they don't show monster effects. I don't think that's what we should be talking about and again, I don't believe anybody said we didn't see an effect. We believe they're effective and it was just underpowered, the studies were just underpowered, period.

MARY TINETTI: Fair enough, I think that was a useful discussion.

We're going to now move on to part B which we will actually be voting on and before we vote, make sure that we all are comfortable with what the question is. It's, as presently written, is it permissible to extrapolate data, remember extrapolation is purely for efficacy, not for safety, not for dosing, although I think Dr. Cnaan appropriately noted that it's hard to separate dosing from effectiveness from adults to children or from older children to younger children for the cough and cold indications for the common cold.

I think for point of clarification,

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we've already identified children as 12, 12 and under, perhaps as we clarify this question, I'm not sure what, are we talking about from older children being 12 year olds or now being children over -- 12 or now that we've identified it as 12, can we clarify what age groups we're talking about here before we address the question.

JOHN JENKINS: I think it would be fair for you to consider extrapolating data from above 12 to under 12.

MARY TINETTI: Okay, fair enough, okay.

JOHN JENKINS: Because older children could be considered some of those adolescents who have actually been studied in the over 12, so I think over 12 to under 12 and then you can later decide if your answer is yes what age groups that you think that's reasonable for.

MARY TINETTI: Okay. So we, can we have some discussion then about the appropriateness of extrapolating data, again, we have I think the general idea here is that there is some evidence of

effectiveness in, in adults.

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Okay. Dr. Dure.

LEON DURE: Yes, I just would ask a question of Dr. Jenkins regarding the term permissible. I mean legally I guess or according to the rules it is certainly permissible, do you mean, is there a better term for this? I mean is this scientifically rigorous or is this socially acceptable, I'm just not too clear on that.

I guess the other question is could you give us some idea of what impact that has in terms of extrapolating, I mean why is this desirable to extrapolate?

JOHN JENKINS: I think in response to your first point, permissible may not be the best word, maybe a more appropriate word would be appropriate, is it appropriate or do you recommend, I mean we're really asking for an affirmative yes or no vote in, for these drugs that are in the monograph, do you recommend or do you think it's appropriate to extrapolate efficacy demonstrated in 12 and above to children 12 and, 12 and below.

So you may want to change permissible to

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some other, some other word. I've forgotten your second question, I'm sorry.

LEON DURE: Well just more of a thought question, why would we ever want to extrapolate?

JOHN JENKINS: Well I think Dr. Nelson tried to get to that earlier, we want to conduct studies in children only when we think we're answering questions that can't be addressed in some other way, so if you're comfortable that the extrapolation can occur from adults to children, then you don't need to engage in that clinical trial research in children. Was that a fair way to --

SKIP NELSON: It is, but let me just make one point of clarification. My stating the reasons that principal extrapolation is important to pediatric drug development should not be interpreted to mean that doing a trial in this condition which is clearly minor and self-limiting and involves

drugs of modest efficacy and modest risk, again something you need to discuss whether that's true of all age groups, et cetera, is not to mean that doing such a study would be unethical. I'm not saying

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that.

And in many ways it's a scientific question as to whether or not the 8 year old is like the 12 year old or the 14 year old as the 2 year old the same as the 6 year old. I mean I think that's part of what the question of extrapolation goes to.

It does have an impact, though, on the studies that FDA may or may not require based on your advice of industry, which is a practical outcome of your scientific deliberation.

MARY TINETTI: Thank you.

Dr. Griffin.

MARIE GRIFFIN: Marie Griffin. It seems to me there should be some compelling reasons for extrapolating and I think we're all searching for what those reasons are and haven't really found them and so since it's a permissible statement or may, I would say that in this situation the body of evidence in adults is not that great. We don't really have a good idea of effect size which we need for risk/benefit analysis, so I, I think, and so I think there are compelling reasons why we would like

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the efficacy data in the children themselves and I see no reason why we should have to depend on adult data in this situation.

MARY TINETTI: Thank you.

Dr. Joad.

JESSE JOAD: Yes, I wanted to speak to the similarities of colds between adults and children. I think we know that the same viruses that cause a cold in an adult can cause bronchiolitis in a young infant or child and can cause croup in a young infant or child, so we know for sure that in those two instances they're not the same and what exactly happens between 4 and 12, I think we just don't know.

And as a general comment about whether

extrapolation is a good idea, I would concur with the American Academy of Pediatrics that children are just not small adults and that there does have to be a compelling reason not to do the study in children. My area of research has to do with the exposure of air pollutants to young animals and it really depends on when you expose them to the pollutant,

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what kind of immunologic, physiologic and anatomic changes you get.

So I think it's, I think it's probably not, because you asked general policy, I really think it's not a good general policy for extrapolation to be the rule and that there should be compelling reasons to do with ethics, perhaps.

MARY TINETTI: Thank you.

Dr. Calhoun.

WILLIAM CALHOUN: Thank you, Bill Calhoun. So it seems to me relevant to that first sub bullet point when extrapolation would be appropriate, it seems to me that one would extrapolate only when there's a data vacuum, when for some reason or another it's not possible, not appropriate, not ethical to obtain the data in kids and in fact we have data in kids that suggests a lack of efficacy. And so I, I don't, I agree with Dr. Joad, I don't think there's a compelling reason that the metered efficacy data could or should be extrapolated.

I disagree a little bit with Dr. Joad in

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terms of the similarity and differences and clearly there are some differences in the response of adults and kids to viruses. Clearly there's some, some differences in the response to pollutants and particles, et cetera, et cetera, but I think by and large the pathophysiology is similar enough that it might be scientifically appropriate, but once again I think that extrapolation should be performed only when there's a data vacuum and we're not in that setting right now.

We have evidence of six studies, some of which may be underpowered, some of which may have

used blunt outcome measures, but the fact is that we do have a number of published studies that do not demonstrate efficacy, so I don't think we're in the situation of a data vacuum.

MARY TINETTI: Thank you.

Dr. Atkinson.

PRESCOTT ATKINSON: Yes, I just wanted to, Dr. Jenkins alluded to the fact that we might want to break this down into sort of different age ranges and also Dr. Joad was mentioning that the

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pathophysiology of the disease may be different in young children and I would be a lot more comfortable extrapolating from adults and older to children to children in the 4 to 6 age range, for example, than to a 6 month old.

So it might be that we should consider children under 2 perhaps in a different light or perhaps separately.

MARY TINETTI: Okay. I think when we get back to the questions we'll have to clarify the age groups that we're talking about because there may be different answers for the different age groups. I think we'll need to come back to that.

Dr. Parker.

RUTH PARKER: Just --

(Please pardon the interruption, your conference contains less than three participants at this time. If you would like to continue, press star 1 now or the conference will be --)

RUTH PARKER: Ruth Parker, I was going to specifically ask that we put in here from older children to children less than 2 as a specific for

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that very reason, so it was just kind of a clarity thing to get us to more concrete information.

MARY TINETTI: Yeah, I'll make a proposal for the question when we get to the question.

Thank you.

Dr. Goldstein.

GEORGE GOLDSTEIN: I think that extrapolation is, and I come at this first of all

from a context of being probably one of a handful of people in this room who actually delivered data, who sat in on the deliberations of the cough, cold panel in 1975, 6, 4 and so on. Tons and tons of data reviewed by experts and then submitted for further review with a pediatric expert Committee.

I remember carrying the stuff and, as well vividly in the days before computers. And I think that extrapolation under the circumstances and context that Dr. Jenkins outlined before is imminently sensible. It may not be quite as sensible today, but there is a lot of data in, on these individual ingredients that was reviewed and I

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should say scrutinized and scoured by that cough, cold panel and its successors and associated committees during that era.

And when they arrived at a conclusion that something was GRASE, Generally Recognized as Safe and Effective, it was a pretty solid conclusion.

Now, there's also two other bits of evidence that you've heard here today for at least this data providing a presumption of evidence and there's no question, none whatever, that a, that pk studies will certainly better inform the extrapolation or any extrapolation that is done.

No question about the technology is different, et cetera, et cetera. We know a great deal more than we knew 30 years ago, but that does not provide justification for simply disposing of what happened 30 years ago as being, you know, of no value.

But the two bits of evidence I would allude are not only that cough, cold panel, but as I keep reminding everyone, the repeated purchase and

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use by not only the child community, but the adult community as well. It works and what we need to do now is to do pk studies and the other elements of the program that were outlined by Dr. Suydam to bring this up into the modern era. 30 years is a long time.

MARY TINETTI: Thank you.
GEORGE GOLDSTEIN: Thank you.
MARY TINETTI: Dr. Gorman.
RICHARD GORMAN: I think it was acceptable to extrapolate data from adults to children when you started this process 30 years ago. I think there's now data that the Committee has stated a lot more eloquently than I can that calls that into question at this particular time for this particular condition, so I think the answer is no, for cough and colds today.
MARY TINETTI: Thank you.
Dr. Cnaan.
AVITAL CNAAN: Extrapolation is an indirect -- oh, I have to identify myself, Avital Cnaan. Extrapolation is an indirect way of reaching

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a conclusion by applying data from a variety of sources to extrapolate.
In this particular case we have the possibility of directly testing, measuring, studying what we're interested in doing. I don't see the justification of extrapolation in this particular context when we can have direct evidence yea or nay do the products work.
I do see the justification of extrapolation in some of the conditions that Dr. Jenkins mentioned that it has been applied like in organ rejection or complicated skin and skin structure infections which are more rare and it would be very difficult to study in children when there's very few children.
So I don't think that it is our charge to conclude about extrapolation outside the cold situation and in this situation I think it is not justified.
MARY TINETTI: Thank you.
Dr. Ganley.
CHARLIE GANLEY: Yeah, I just wanted to

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make a point about the efficacy based on some of the comments is that all the efficacy data in OTC drugs is, you know, pretty lousy and I just don't believe

that's the case. I think even if you, I worked in a prescription side for 10 years before I ended up over here and to think that prescription drug products have profound treatment effects is a misrepresentation of the facts.

You're generally dealing with a 15 percent or 20 percent or 25 percent treatment effect and so to state, to mischaracterize I think OTC drugs and lump them into this that we accept minimal data I just don't think is an accurate characterization because seeing what's also been done on the prescription side, the process works the same way.

And so I just wanted to make that point.

MARY TINETTI: I don't think, I wasn't hearing that we were saying that the OTC data was.

CHARLIE GANLEY: Well I think it was characterized as meager data and things like that.

MARY TINETTI: But I think we did agree

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that it was modest but we certainly wouldn't argue that the standards for the prescription drugs are any better. We'll certainly grant you that.

Dr. Nelson.

SKIP NELSON: I'm Dr. Nelson. It would be helpful in the course of people giving their answers to the question of extrapolation I think to hear more about the two criteria for extrapolation, meaning the course of the disease and response to treatment, why is an ethicist suggesting that.

One of the principles of ethics is justice is fairness. One of the questions is the fairness of applying the principles of extrapolation in pediatric drug development, so even though the studies may be ethically designed, even though they may be doable with appropriate end points, the question is how should one apply the principal extrapolation with some fairness.

And all I've heard, for example, is less than 2 carved out, but I didn't hear the 2 to 6, the 6 to 12 and so I think there needs to be more discussion and particularly around the course of the

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disease and the response to the treatment to allow a fair application, if you will, of the principal of extrapolation.

MARY TINETTI: Fair enough, I think that's also a scientific as well as an ethical point and I think that would be very helpful if people responded to those two points. That's an excellent point.

Dr. Neill.

RICHARD NEILL: No, I don't think extrapolation is appropriate in this circumstance, but I want to speak to some of the issues that you've asked us to consider with regard to the pathophysiology.

We heard yesterday I think some compelling reasons why children are not adults, why the disease process specifically when looking only at the pathophysiology may not be the same, why a virus in an adult taken and put in a child might behave differently.

But I have to say I'm discomforted by the lack of attention to some of the greater issues,

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if you will, the need to add on to what I view as a somewhat reductionist approach, looking at one virus in one child in only one indication for one entity when, in fact, the reality of the marketplace is we've got data from studies that include combination medications that are used for end points that may or may not be clinically meaningful and which show, even given these dubious clinical end points, lack of efficacy, specifically, you know, we know that kids get sick, they go to school, they get sick. They bring their colds home to all their parents who hopefully have gotten immunized against some of this stuff by virtue of the earlier children that they've had, but it's not as if the use of the medication in the one child for the one cold is going to determine the overall benefit in that family or in that community.

There are some real public health issues that have to do with the amount and type of these entities that are being used, whether in single dose

form or in combination form and I think there are epidemiologic data that need to be considered that

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look at an N greater than 1 where it's not simply that child, but that child's family, that child's classroom, that child's community that have to do with efficacy and at what price.

I've been in a couple of these meetings now and I'm pleased to hear Charlie mention the caveat regarding data about prescription drugs as opposed to OTC, given that many times the deliberations we've been asked to take part in have to do with switching from prescription to OTC, which involve a lot of conversation about the imagining what happens both in the minds of patients and in the minds of physicians and perhaps more importantly in the minds of prescription benefit managers when a medicine which has been around and has a body of data magically changes from requiring a prescription to not a prescription. And, you know, it sounds like, Charlie, what I heard you say is, gee, the data's not even that great for some of the things that are available by prescription.

Given that general statement that I hope I haven't mischaracterized, and which, you know

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obviously it can be taken exception with, it's pretty clear that the efficacy for this, these number of entities is not compelling and, again, you know, just to summarize, I think that that criteria that you've asked us to consider just for extrapolation, to look at whether the pathophysiology is different in adults and children, we need to take into account some of the epidemiologic and public health implications more than just that single child data.

MARY TINETTI: Thank you.

Dr. Rappley.

LAURA MARCIA RAPPLEY: Yes, thank you. I would like to suggest that it's appropriate to rely on extrapolated data for a limited period of time and I'm just saying, for example, two years, during which we expect efficacy trials to be

completed. And I would agree that it's really important to look at population health studies that can describe the impact of these, use of these meds on public health issues as well.

I just wonder what people would think

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about that, about the time frame, about accepting extrapolated data for a period of time and then expecting to see some results from more definitive work.

MARY TINETTI: It might be worth asking FDA, is that even a feasible option for us?

LAURA MARCIA RAPPLEY: Yes, right.

JOHN JENKINS: I think I'm going to have to ask Dr. Rappley to expand on that. You're saying, kind of saying it's okay to extrapolate now but we're giving you two years to come in with data; is that what you're suggesting?

LAURA MARCIA RAPPLEY: Well, I'm, I'm wondering if we say it's not appropriate to extrapolate -- to use extrapolated data, there would be repercussions in terms of a use of these meds and access to these meds and are we ready to make recommendations about restrictions on the use of these meds or would it be worth considering saying -- an approach in which we say we will allow the extrapolated data to, or we assess the extrapolated data at this point in time and though

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we're requiring something more rigorous two years from now, we would rely on that data to allow use of these meds or recommend use of these meds -- or availability of these meds, not use of these meds, for the next two years, but we look for definitive studies because we believe, one, they are possible and, two, with very wide-spread use of these medications, they are necessary.

JOHN JENKINS: Yeah, I think on question three we get to asking you, you know, what needs to be done now. These monograph products are regulated through rule-making, so the rule-making process takes considerable amounts of time, as you all know, so even if you recommend that extrapolation not be

used in this, this set of drugs for children, we have to go through a rule-making process to actually change the labeling and get to that final end point which will take time which kind of effectively does what you just described, but we're also asking in question 3 there are other mechanisms we might want to pursue.

If you're telling us we really don't

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think these should be available anymore for children under such and such age, then we would have to work with the industry to try to affect those changes in a much more timely manner than we can through the rule-making process.

MARY TINETTI: Okay, thank you.

Maybe just go a few more, because we want to get to the vote. So I guess if any comments are really new or additional comments, not necessarily repeating what we've already heard. So if people have really new comments to make.

Dr. Newman.

TOM NEWMAN: Yes, similar to what Dr. Cnaan said, but I think the key point is to extrapolate when it's not ethical or feasible to do the randomized trials, and this is one of the troubles I have with the rule under PREA, it doesn't seem to consider that at all.

It says when the course of the disease and the effects of the drug are sufficiently similar in pediatrics and adult populations, but you usually won't know if the effect of the drug is similar in

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pediatric populations unless you actually do the study, so. And the feasibility doesn't seem to enter into it, but in the case of colds, and I would also argue for allergic rhinitis where there are hundreds of thousands of children potentially taking these medicines or millions, it is very, very feasible to do a randomized trial and see whether the effects of the drug are similar in children.

So I do think the feasibility and ethics are very important, not just judgments or guesses about ability to extrapolate.

MARY TINETTI: I think implied in your point which is one of the things we're asked to comment upon which is response to treatment and your point is that, I mean implied in your statement is that we don't know the response to treatment, whether it's the same and that would be the reasoning for, for not extrapolating. Thank you.

Dr. D'Agostino.

RALPH D'AGOSTINO: Yeah, I can be brief. I thought, you know, yesterday when the presentations were being made to us there was a lot

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of physiology in development going on in terms of the children and I would love to have some, though we don't want to prolong this, but I would have loved to have had some discussion of that on the part of the panel, is there really physical differences that preclude this extrapolation.

And I think we were probably just agreeing with some of the things that were presented to us and certainly under 2 it certainly looks like a real problem, but it doesn't seem to me it was very clearly stated from 2 to 12.

The other comment, I want to make two brief comments that the nonprescription drugs go through a very rigorous process and I do want to emphasize again that some of the studies I was involved with there were actually a 50 percent reduction of symptoms with these antihistamines and so forth, so it's not a trivial difference.

And then lastly in terms of the cough, cold panel, I became involved with the, these products when the cough, cold panel had a category 1 that they put out and with the screaming and yelling

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on the part of different groups responding to the category 1 which says it was safe and effective, the Agency turned it back to a category 3 and so nothing was cast in stone by this Committee.

The Committee knew when it was sending its recommendations that they would have to be examined over and over again and us examining one thing again is certainly not out of line and I think

very appropriate. And certainly this extrapolation, I was involved in a lot of those over-the-counter review panels and we just through all the pediatrics to it's, to the pk, we just didn't face, we didn't have any data and we knew that sooner or later somebody was going to have to worry about it but it was just sent off to pk and now is the time to start worrying about it.

MARY TINETTI: Thank you. I think our final comment, Dr. Bier.

DENNIS BIER: Yeah, Dennis Bier, you know, I -- the, the extrapolation is just another word for expert Committee opinion and in 1972, experts in the evidence-based hierarchy, expert

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Committee opinion was at the highest level, in 2007 it's at the lowest level of the evidence-based hierarchy and Mark Twain said, one of my favorite quotes, "Supposin' is good, findin' out is better."

And I, you know, we're not, again, to go back to what Tom said, we're not talking about subjecting kids to cardiac catheterization, you know, heavy doses of radiation, we're talking about essentially noninvasive studies to find out efficacy and I just don't see that there's any reason to extrapolate data.

MARY TINETTI: I think we'll move on to, to voting on this but I think before we do that I think we do need to clarify the age groups that we're, that we're talking about here and I think it was, I can't remember who was it raised the points about age, but I know Dr. Parker did and Dr. Atkinson, so perhaps you would each propose an age for us to address here.

Dr. Atkinson.

PRESCOTT ATKINSON: Prescott Atkinson, UAB, I would propose that we would consider the 2

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to, 2 to -- over 2 or 2 to 12 year old age group and then under 2 separately for this question.

MARY TINETTI: Okay, so you would be saying can we extrapolate from adults to under 2 and then can we extrapolate from adults to 2 to 12? Is

that your proposal?
Any discussion on that? Can we agree on that, is everybody agreeable on those, that designation? Okay.
Okay. Dr. Parker.
RUTH PARKER: If it's under 2, it might should be under 12, I mean, you know, it's kind of, you know, you get into how you write the label and how you end up interpreting and peoples ability to understand the difference from --
MARY TINETTI: To 2 to less than 12.
RUTH PARKER: Well I just point that out just to be very clear on it, I mean, you know, it's a flip of a coin, it's a birthday, but there you go.
JEFF ROSENTHAL: I'm not clear on the distinction we just made, what's, do you mind just reviewing what we just decided.

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MARY TINETTI: Right, I think there was a point raised about ages and the question is pretty general, can we extrapolate from adults to children, young children and adults to older children. I think that was just a point clarifying what we mean by younger children and older children.
So the question is can, so rather than just sort of generically saying can we extrapolate from adults to children, there's a proposal to say can we extrapolate from adults to children less than 2, yes, no, and then can we extrapolate from adults to children 2 to less than 12.
JEFF ROSENTHAL: Jeff Rosenthal, my, I'm concerned that the 2 to 12 age group is, there's a lot going on developmentally in terms of changes in kids' physiology. It seems like that's a pretty broad age group to consider extrapolating data and drawing analogies from that.
MARY TINETTI: So what would you propose?
JEFF ROSENTHAL: I like, I'm a split in this regard, I like the, I like much smaller groups,

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so I don't even like the 6 to 12 group.
MARY TINETTI: I think we have to be a

little practical.
JEFF ROSENTHAL: I'm philosophically a bit opposed to this concept anyway, but, you know, I don't know, 10 to 12, 8 to 10, 6 to 8.
MARY TINETTI: Well I think perhaps, perhaps it may make more sense to see what the vote is in general, because if the vote is not in favor of extrapolation, it may be a moot point, so perhaps we can come back to your point after the vote?
JEFF ROSENTHAL: That sounds fine, yeah, that sounds good.
MARY TINETTI: Okay, so can the vote be less than 2 and then 2 to less than 12 and then we can take your point. Okay.
All right, let me read the question as I think we have adapted it. Is it appropriate to extrapolate data from adults to children less than 2 for the cold and cough indications for the common cold, yes or no.
If that's everybody's understanding of

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the question, of those who are in favor of extrapolating from adults to children less than 2, raise your hand. So that's zero.
So then let me read it for the older children, is it appropriate to extrapolate data from adults to children 2 to less than 12 for cold and cough and cold indications for the acute cold.
Anybody in favor, yes? Okay.
Dr. Atkinson, what, he has to state his name? State your name and say yes.
PRESCOTT ATKINSON: Prescott Atkinson, yes.
MARY TINETTI: All the nos? Okay.
LAURA MARCIA RAPPLEY: I'm voting no.
MARY TINETTI: Okay, we'll start with Dr. Rappley, can you just give your name?
LAURA MARCIA RAPPLEY: Marcia Rappley and I'm voting no, it is not appropriate.
MARY TINETTI: Okay, we'll start with Dr. Calhoun.
WILLIAM CALHOUN: Bill Calhoun, no.
TOM NEWMAN: Tom Newman, no.

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MIKE COHEN: Mike Cohen, no.
JESSE JOAD: Jesse Joad, no.
ROBERT TAYLOR: Robert Taylor, no.
MARIE GRIFFIN: Marie Griffin, no.
JAN HEWITT: Jan Hewitt, no.
WILL SHRANK: Will Shrank, no.
RALPH D'AGOSTINO: Ralph D'Agostino, no.
BEN CLYBURN: Ben Clyburn, no.
RUTH PARKER: Ruth Parker, no.
MARY TINETTI: Mary Tinetti, no.
DENNIS BIER: Dennis Bier, no.
AVITAL CNAAN: Avital Cnaan, no.
RICHARD NEILL: Richard Neill, no.
AMY CELENTO: Amy Celento, no.
ROBERT DAUM: Robert Daum, no.
LEON DURE: Leon Dure, no.
JEFF ROSENTHAL: Jeff Rosenthal, now that I understand the issue, no.
SEAN HENNESSY: Sean Hennessy, no.
MARY TINETTI: Okay, thank you. So I think that might make the next part of the questions mute, comment on when extrapolation would be

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appropriate and when, in addition, pk studies should be conducted. If it was a no vote for extrapolation, I think that becomes a moot point.

So I think we can move on to question C which is presently written if extrapolation is not considered appropriate for cold and cough indications for the common cold, please describe the data needed to demonstrate efficacy in children, for example, what clinical studies in children with clinical end points be necessary to support efficacy in children, yes or no, and if the trials are determined to be necessary, please comment on which ingredients and for which age groups.

So again, this is, this is efficacy at this point, not safety. We'll be moving on to safety in the next question.

So perhaps we'll have some general discussion there and perhaps that will help us clarify and specify the question.

Dr. D'Agostino.
RALPH D'AGOSTINO: Ralph D'Agostino. The sponsor yesterday made a presentation saying

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well they did have a plan to look at pk studies for doses and then move on to clinical trials and I think that that made a lot, to me it makes a lot of sense and I would sort of endorse that.

I think they do have to worry about the condition that they're looking at, the virus, question about virus type or just general common colds. I think the question about the population, I think issues like the cold should be no more than a couple of days old is important. I think the treatment, from what I hear, should be single ingredients rather than these multiple ingredients. I think then you have a real issue of pediatric outcomes that they have to have outcomes that are appropriate in children. I think the frequency of the measurement and do you take it multiple times during the day in terms of symptom relief or do you wait for a couple of days.

I think all of these things have to be faced and I think that the studies, judging from the adult population, the effects are going to be small that you're going to need a couple of hundred per

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group to run these studies, but I think that there are lots of children and lots of parents who would probably be quite willing to have their children involved in these studies. So I think that a clinical program, clinical trial program is quite feasible. Certainly I endorse it.

MARY TINETTI: Thank you.
Dr. Cnaan.
AVITAL CNAAN: I agree, Avital Cnaan, I agree and won't repeat what Dr. D'Agostino just say. I'd like to add on the pk front that Chlorpheniramine is not studied in children under 6 years old in pk and that should be added in the pk study.

I would also, based on the materials we've been seeing, suggest that any combination

product that is marketed should have an accompanying appropriate pk study and then depending on the result of those, that would inform what other later clinical efficacy studies will or will not be needed in the combination products.

MARY TINETTI: Thank you.

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Dr. Parker.

RUTH PARKER: Two comments, one I would say that the studies need to be on single ingredient and there needs to be discussion about single ingredient products rather than combination products overall and the studies are going to be a lot more useful if they're single ingredient because you can look at, you know, the effect of that single ingredient.

The second is a point of clarity again to demonstrate efficacy in children, I would like to talk about whether or not that is all children including children under 2 or if that is for children that are 2 to under 12?

MARY TINETTI: Thank you.

Dr. Griffin, did you, I think you had your hand up.

MARIE GRIFFIN: Yeah, I think yesterday we talked about some other end points like airway resistance and the problems with end points and I think, I would just like to say that I think we need the kind of end points that lead parents to buy

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these products and not surrogate end points or other types of end points so that if we -- if there was a decrease in airway resistance but there was no change in symptoms that lead parents to get these products, then I don't think that that's very useful.

MARY TINETTI: Would you like to suggest some of the end points that it should be including?

MARIE GRIFFIN: Right, so the reasons why parents might want to get the children these medicines may be because they have a runny nose or they're fussy or they're coughing or things like that.

MARY TINETTI: Dr. Clyburn.
BEN CLYBURN: Ben Clyburn, one thing that, one thing that I think should be in there that we didn't talk a whole lot about yesterday when we looked at specifics of clinical trials is one of the imputed benefits of these medicines and one of the downsides are sedation and sleep. And as a parent of five, being able to sleep at night may be a benefit, but over-sedating your child is not and I

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think that we need to separate sleep and sedation out from some of the other.
MARY TINETTI: Okay. Thank you.
Dr. Neill.
RICHARD NEILL: I have difficulty answering this question in part because the manufacturers of these entities are going to be faced with coming up with clinical end points for a product that will end up on a shelf next to vitamins, supplements, homeopathic remedies which despite in treatise against making specific health claims make specific health claims well, enough that my patients come to me saying I'm taking this product A for this cold, what do you think.
And when I go into the marketplace and look at that aisle, some pictures of which we saw yesterday, I see these same products and as a parent, having to choose amongst these different entities, it distresses me that the regulatory landscape is such that this small group of six or eight entities is going to be subject to that monograph process we've heard so much about and be

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compared against a group of entities that are subject to the NDA and compared to a group that the FDA has nothing to do with.
And this latter group includes a lot of products that have a clear statement on their box which says the FDA has not made any assessment of the claims that we're making, it's typically in small italicized print that Dr. Parker might want to comment on with regard to literacy and how you get the message across.

I guess the overall concern that I'm raising is we're trying to answer a very important question what clinical end points would be necessary in efficacy trials and we're going to take that data for these specific entities, apparently without regard to all of the other potential end points that parents might come to in terms of that choice, what can I use to help my children feel better.

So to the extent that we adopt any clinical end points, I just want us to keep in mind that that's not the only issue here. I realize it's not within the scope of FDA, perhaps, but it

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has continued to be a theme at some of the meetings and it's going to be a theme in the drug store shelves until it gets addressed.

MARY TINETTI: Do we, did FDA want to comment or just duly note?

CHARLIE GANLEY: Well I think the issue with dietary supplements is in a different center within FDA and under different regulations, so I don't want to take on that and I think Dr. Neill is correct in the challenges for consumers, but we sort of have to live under the rules that we regulate drugs and hold them to the standards that we require and it will be applicable for a monograph as well as NDA marketed OTC drugs, okay, where they may have some of the claims for common cold that had depended on, you know, a historical finding through the monograph process where NDAs subsequently got approved with the, some of those similar ingredients, so they would have to be held to the same standards.

MARY TINETTI: Thank you.

Dr. Bier.

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DENNIS BIER: Yeah, Dennis Bier. It's, you know, I realize that determining the end points can be a difficult issue but it seems to me, you know, that we start with what's on the package and what's in the advertising. I mean if it's being sold for cough, one of the obvious end points is cough, I mean we have a list of things that these

products are being sold for and we should at least determine whether those indications are correct or not.

MARY TINETTI: Dr. Goldstein.

GEORGE GOLDSTEIN: Just a general comment to the panel as a whole and that is the industry has certainly stated its support for studies and will, I'm certain, honor that commitment, but we all have to keep in mind that there are financial realities facing these companies and it is not a let's do everything up to, you know, hundreds, thousands of thousands of patients. It cannot be an unlimited task and I'm sure you realize that.

The other comment I would have would be

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to Dr. Parker with regard to single ingredients, it reminds me a little bit of the Wrigley chewing gum commercial, only this time it would be double the risk and double the cost. The single ingredients, if put in the hands of parents, et cetera, there is a risk and I think we must all be cognizant of that risk and the cost is, of course, goes along with, with it as must be obvious.

Thank you.

MARY TINETTI: Thank you.

Dr. Joad.

JESSE JOAD: Yeah, I just want to make sure it's clear that I think single ingredient is the only way to go. You have to look at an antihistamine and then probably a runny nose, you look at a decongestant, you look at a stuffy nose, you look at an antitussive and say number of coughs, maybe severity of cough and I'm not sure what you'd do with Guiffasen, but quality of cough or something, but they should be very clear end points that are pathophysiologically related to what the drug is expected to do studied one by one in

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children and anything short of that I think would be, you know, not useful information for us. Then you can start putting them together and do the things that we're discussed.

MARY TINETTI: Thank you.
Dr. D'Agostino.
RALPH D'AGOSTINO: I think the issue of single ingredients was raised at least when I raised it in terms of the clinical trials. I think you do need, as just an endorsement was said, that you do need single ingredients. I think there's another discussion in terms of do you move then to multiple ingredients and then what do you actually package for the consumer.
I, all of those steps have to be put in place but I think we're all, I think a number of us are saying if you try to do a multi-symptom clinical trial, you're running into a lot of trouble. And if I recall correctly, and the FDA can correct me on it, when we were looking at these multiple ingredients and so forth, we actually were running single ingredient studies and then sort of putting

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them altogether and it was consumer studies that said that people get these things jointly and so forth that was driving, that was actually driving the multiple ingredient products.
So I think we are sort of facing that issue with single ingredients for the clinical trials.
MARY TINETTI: Thank you.
Dr. Calhoun.
WILLIAM CALHOUN: Bill Calhoun, so first to amplify, I agree that single agents are the way to go.
To the question of age group, I think that it's important for us to recognize that the further away children are in age from adulthood, the more likely they are to be different.
And during childhood, lung growth continues perhaps to the age of 8 or 9 years, it's clear that there are differences in airway geometry, nasal airway geometry, pharyngeal airway geometry in infants, so I think as trials are developed it's critically important that the end points be selected

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that are appropriate for the age and that the ages

are separated into pathophysiologically uniform age groups.

The fact is that viruses affect epithelial cells and one who has a burst of innate immunity and one has acquired immunity and all of that is probably similar across age group with some differences perhaps in the developmental immunology, but I think the geometry of the airways is a fairly big deal and so the clinical end points that are appropriate may be quite different depending on the age of the --

MARY TINETTI: Would you like to suggest what some of these might be?

WILLIAM CALHOUN: I think the pediatricians would probably have more specific information, but I would certainly think that under 2, 2 to 6 and 6 to 12 would be a broad lumping that might be appropriate.

MARY TINETTI: I mean that's a good point, does anybody want to discuss, we'll get back to you, Doctor, in a minute, but this point,

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different end points for different age groups; this some -- any, any comment on that?

Dr. Ganley.

CHARLIE GANLEY: Yeah, I think it's worthwhile to take a vote on this, you know, question about whether clinical trials and then try to get a sense as to, you know, whether -- and it gets to the points just made as to whether there's ever, you know, if there's a clinical trial done in a 6 to 12 year age, can that be extrapolated down to 2 to 5 and I think it gets to your point, it would be helpful for us to get everyone's opinion on that. Okay.

MARY TINETTI: Fair enough, so to use one --

CHARLIE GANLEY: Because that was part of the question of 1B where it said older children to younger children and it goes back --

MARY TINETTI: Right.

CHARLIE GANLEY: So that if we can treat that as two separate.

MARY TINETTI: So you just want a yea,
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nay on the clinical studies first, on the need for clinical studies first.
CHARLIE GANLEY: Clinical studies.
MARY TINETTI: Sure.
CHARLIE GANLEY: And then in which groups would you want a clinical efficacy study versus, you know, it may say in all the groups or you may say that we would accept it in a 6 to 12 age and extrapolate to younger ages or under 2 you have to do a study or, you know.
MARY TINETTI: I think the point that Dr. Calhoun was getting at, not necessarily the age groups, but what, getting at the point of what the end points might be, but we can certainly vote.
CHARLIE GANLEY: Yeah, I think those are things that really we're not going to solve today, actually, I think we're going to have to take that back and come up with something.
MARY TINETTI: Okay, fair enough.
CHARLIE GANLEY: But I think his point is well taken.
MARY TINETTI: Okay, let's do a couple
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more comments and then we'll do the vote.
Thank you. Dr. Newman.
TOM NEWMAN: Tom Newman, I vote yes that the clinical end points are necessary.
MARY TINETTI: We're not voting yet.
TOM NEWMAN: But for what the end points would be, I think certainly it should be the things for which the drugs are marketed for or for which the goal of the parent is in treating the child and I would make, at least for me in terms of whether, if these studies were done and it would be sufficient for me to recommend them, I would want to know not only things like cough counts and weight of mucous or, even, does it seem like the cough is getting better, but the level of the child's discomfort.
I thought Dr. Walson's slide 22 made a good point where he says that the treatment is to

make the patients feel better and when I see, I see a lot of kids with colds who really are not very uncomfortable from the cold and the parent is seeking some sort of guidance or reassurance, but I

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don't think we need to give, we want to give the message that just because the nose is running we need to use a medicine to stop it or just because the child is coughing we need to stop it.

The purpose of the treatment is to relieve discomfort from the runny or congested nose, relieve discomfort from the cough and I think there's a real analogy with fever there, we don't, at least in our teaching we don't say every child with a fever from their URI needs to get anti-pyretics, the reason to treat with anti-pyretics is to reduce discomfort.

And so I would want to see, you know, not just efficacy end points in terms of just, you know, runny nose and cough, but some measure of the child's discomfort, because most children with colds, many of them are not that uncomfortable and don't need medicine.

MARY TINETTI: Thank you.

Dr. Daum.

ROBERT DAUM: So I actually think that the Committee is talking about some very exciting

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things now and that this, the potential --

MARY TINETTI: We weren't before?

ROBERT DAUM: I'll leave that one alone.

I think that the opportunity for research into the symptomatic and perhaps even more things could be combined with it besides symptomatic, relief of, one of the most common problems that afflict children is potentially very, very exciting to get real data about this, so that if industry is going to lead the studies, I would urge them up front to get collaboration from stakeholders like pediatricians, like virologists, people at the NIH. I mean there's lots of people one could conjure up.

But I want to emphasize something that

Dr. Joad mentioned before and that is that it would be very important to define these studies not by just the symptom like cough or just runny nose, but to really consider what kinds of coughs and runny nose we care about in this regard and so that in terms of designing studies which I think is what we're talking about now, I would be very careful to

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not put apples and oranges into the study eligibility group and try and spend time thinking up front what it is we care about, which cough and which runny nose and look at those and perhaps not all.

MARY TINETTI: Thank you. Last comment, Dr. Rappley.

LAURA MARCIA RAPPLEY: I guess I would like to put in, put up for consideration again the population base studies as well. They could look at rates of transmission among groups of children, patterns of absenteeism, they could look at the health care utilization patterns, which is, all of these are sort of suggested or implied that by decreasing symptoms with these particular medications, we can impact some of these larger issue, so I think we do have the ability to examine that through some population and health services studies.

And I would also say this is a place where we could look at that diversity issue so that these larger population-based studies could look at

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not only diversity by ethnicity and socioeconomic status, by diversity in the kinds of settings in which children spend time.

MARY TINETTI: Thank you.

Dr. Parker.

RUTH PARKER: Let me just say as a doctor, what I'd like to know and I'm probably not going to get this out of the clinical trials, but let me tell you what I'd like to know, I'd like to know if my patients are going to do better taking Acetaminophen or Ibuprofen or one of these cough and cold preparations or are they going to do better

taking a combination of the single ingredients, that's what I really want to know, which one is better. That's not how we design in order to get the studies through, I got that. It's a safe and effective use of each individual ingredient, got it.

But if you want to know what I really want to know and what I think would help patients, the most to improve public health about the common cold, that's how I would frame it.

So, in the design of these studies, the

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comment I would make is watch out for what's going to make you feel better, watch out for these internal, what are they called, internal analgesics that do tend to make you feel better maybe if you just take one right now, I don't know.

But think about sort of the face validity and the practical thing of this and what really at the end of the day helps people spend their money wisely.

MARY TINETTI: Thank you. I think, let me propose the question as it's presently written and then we'll take a vote.

Would clinical studies in children less than 12 with clinical end points be necessary to support efficacy in children, again, less than 12 years old.

Then after we do a vote on this, then we can actually discuss age groups and so let's start with that question.

So those who say yes that clinical studies with clinical end points are necessary?

LAURA MARCIA RAPPLEY: This is Marcia,

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Marcia Rappley, and I vote yes.

MARY TINETTI: Thank you. We'll start on this end.

SEAN HENNESSY: Sean Hennessy, yes.

JEFF ROSENTHAL: Jeff Rosenthal, yes.

LEON DURE: Leon Dure, yes.

ROBERT DAUM: Robert Daum, yes.

AMY CELENTO: Amy Celento, yes.

RICHARD NEILL: Richard Neill, yes.

AVITAL CNAAN: Avital Cnaan, yes.
DENNIS BIER: Dennis Bier, yes.
MARY TINETTI: Mary Tinetti, yes.
RUTH PARKER: Ruth Parker, yes.
BEN CLYBURN: Ben Clyburn, yes.
RALPH D'AGOSTINO: Ralph D'Agostino, yes.
WILL SHRANK: Bill Shrank, yes.
JAN HEWITT: Jan Hewitt, yes.
MARIE GRIFFIN: Marie Griffin, yes.
ROBERT TAYLOR: Robert Taylor, yes.
JESSE JOAD: Jesse Joad, yes.
PRESCOTT ATKINSON: Prescott Atkinson, yes.
MIKE COHEN: Mike Cohen, yes.
TOM NEWMAN: Tom Newman, yes.
WILLIAM CALHOUN: Bill Calhoun, yes.
MARY TINETTI: Any nos?
Any abstentions?
Okay. Darrel, can you read the vote for us.
DARREL LYONS: For the record, Darrel Lyons, for the record, question 1B, it was one yes vote and 21 no votes, zero abstained.
Question 1C, 22 yes votes, no, zero no votes and zero abstained votes.
MARY TINETTI: So for the second part, there it was asking us to comment on the ingredients and age groups and this is not something I, as you said, we're not going to be able to design the studies today, but I heard sort of generally sentiments that the ingredients should be studied individually. Unless there's any comment other than that, then I think we can just say that that was our general sentiment.
For, and also that we felt important that it was clinical outcomes that are the symptoms that they're marketed for.
For age groups, I think again before we said less than 2 and 2 to 12. I, I'm not sure that we want to sort of vote on that because it may be

depending upon what we say later, some of that might be a moot point, but I propose that we sort of defer the age, age groups until later.

Is that reasonable? Okay.

So we can move on to the safety issues.

Dr. Cnaan.

AVITAL CNAAN: Just one comment, the way the questions are phrased, the pk issues is only listed in the context of extrapolation. I think I'd like to make the comment that the pk studies have their values for helping in the clinical studies and should not be forgotten in the mix.

MARY TINETTI: So you're proposing that pk studies should be included for all the ingredients in the clinical trials?

AVITAL CNAAN: Yes.

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MARY TINETTI: Okay. Okay.

DENNIS BIER: I wonder whether we shouldn't add that as a separate question or vote. I think that's very important, frankly.

MARY TINETTI: Why don't we go ahead and do that, then it will be on record.

CHARLIE GANLEY: Well I think we're comfortable if we were going to ask for clinical studies, we would ask for pk, I think that's a given.

MARY TINETTI: Okay, that's a given.

CHARLIE GANLEY: And I don't think we need to comment on that.

MARY TINETTI: Okay, fair enough, thank you.

RICHARD NEILL: Just with regard to the age group issue, I, I do think that it's worthwhile just moving forward and not trying to design a study here, but I do want to comment that the data that we've seen so far, that I've seen so far that FDA put together suggests to me that that variable age has been sort of put into this, you know, ordinal

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fashion and it's not clear to me that the studies have universally, and I'm going to look to the two statisticians that hit me when I say something

wrong, okay, I would be interested in any data that looks at efficacy in age, appropriately consider age for what it is, which is a continuous variable and analyze it that way as opposed to boxing these kids into 6 to 12 and below 6. That's, that's it.

MARY TINETTI: Well we'll have a brief discussion of that. Again, I think that, I mean there's, I'm sure there's a lot of issues that go into designing these studies, but a quick comment.

RALPH D'AGOSTINO: Yeah, I was going to say there are a lot of issues, but the bottom line is where we're talking is unless you have the age group in there, you aren't going to be able to make a claim on that age group and we have to face the question if you do it for 9 to 12, can you move down to 9 and under and so forth. We haven't faced that issue at all.

Right now I think we're saying that if you want to make a claim on an age group, you have

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to test that age group.

MARY TINETTI: Is there, is there a motion for a question that you want us to --

RALPH D'AGOSTINO: Well I think it was an interesting question. If we did a, if we ran a study on 2 to 6, would we feel comfortable 6 to 12 is taken care of or the other way around and I think that's -- I'd like, I mean I don't have an answer at all, being a humble statistician, I can't make that question, but somebody -- or an answer to that, but somebody on the table probably can.

MARY TINETTI: Yeah, I think it's just sort of, it's a practical sort of when we, when we make a proposal what exactly are we, are we saying, because you could parse this out in many ways, but I think the point you're making is if you're going to market it to an age group, there needs to be data to support that there, it's effective and safe in that age group; is that --

RALPH D'AGOSTINO: Exactly.

MARY TINETTI: -- is that your point? And I think that says it. Fair enough.

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