DR. STARKE: Now, here is the example of pediatric evaluations performed for Allegra or fexofenadine and the antihistamine that was developed to treat seasonal allergic rhinitis and chronic idiopathic endocardia in children. Allegra was approved for treatment of seasonal allergic rhinitis in patients 12 years or older in 1996.

The pediatric program for SAR in patients 6 to 11 years of age included pK, which showed comparable exposure to adults and for the dose chosen and two efficacy and safety studies with an exposure of over 400 patients. It should be noted that only one of the two studies was able to demonstrate a statistically significant difference between active and placebo treatments, pointing to the fact that even for these drugs, with known efficacy, there may be difficult performing such studies.

For this age range, we have accepted one positive study, relying, in part, on efficacy demonstrated from adults and safety that showed no difference concern from that seen in adults. But as I said, we would accept a program with complete extrapolation from 12 and below. For the SAR indication in patients 2 to 5 years of age and for the CIU indication in 6 to 11 years of age, efficacy

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was fully extrapolated from older children and adults. The programs included pK and safety in all ages with a safety database of over 900 patients ages 6 months to 5 years.

I'm going to switch here now and talk about the development program for Tavist, an antihistamine that was developed a supplement came into us for the treatment of colds in patients 12 years of age and older. Tavist or Clemastine Fumarate is in the ethanolamine class of antihistamines. It's structurally similar to diphenhydramine and carbonoxamine, and it has anti-coallergic activity.

A prescription to over-the-counter switch was approved for allergic rhinitis in 1992 and the prescription supplement came to us in 1996 for the treatment of colds in patients 12 years of age and older. The program included one natural cold study, one adduced cold study and additional information from four natural cold studies. A natural cold study is pretty much what it says it is. This type of study allows the patient to

develop the cold and begin treatment shortly after the cold symptoms begin, whereas induced cold studies are also

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what they say they are or imply. The subject is administered a respiratory virus inter-nasally. In this case, rhinovirus, and the illness is followed over the course of time to observe the treatment affect.

The application was subject to a joint pulmonary allergy and nonprescription advisory committee in November of 1995 and the advisory committee recommended approval of the application, specifically, for the treatment of the symptoms of rhinorreha and sneezing in adults and children 12 years of age and older with a common cold.

Here's a brief description of the natural cold study, a study design that probably could be adapted to evaluation of colds in all age group. Patients are randomized in advance and begun on study treatment within 24 hours of the start of the cold symptoms. In this study 403 patients were randomized to placebo or active treatment. Severity of symptoms, of sneezing and rhinorreha were captured over the course of the illness. The primary efficacy end point was a comparison between Tavist and placebo for change in baseline, which was Day 1 to Days 2 and 3 for the two symptoms.

Here are the results. As expressed by treatment

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group means for the ITT population, the table shows columns for the study day on the left, each treatment, difference between treatments, and the P value for each day, both sneeze and rhinorreha are shown because the primary end point compared reflective scores on Days 2 and 3, with instantaneous scores obtained on Day 1. I haven't shown you that. Rather I've shown the results for each symptom over the course of treatment out to Day 4. For sneeze, the results were significant on Days 2, 3 and 4. For rhinorreha, the results were significant on Days 3 and 4, with a trend on Day 2.

So in summary, I've taken you through our thought processes for extrapolation of efficacy for prescription drug products reviewed in our division. I've taken you through the decision tree for extrapolation, many of which are listed here and illustrated by the Allegra example. While PREA applies to NDA and BLA applications, the

decision tree is really applicable to extrapolation of most systemically active drugs.

Additionally, I've presented the example of Tavist and antihistamines studied for cold indication in patients 12 years of age and older, illustrating the type of study

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one might consider if studies for cold indication were considered necessary. Thank you.

DR. LOPEZ: Good afternoon. My name is Lolita Lopez and I'm a medical officer from the Office of Nonprescription products. I'm also a pediatrician.

My presentation will focus on the safety and efficacy of OTC cough and cold products in pediatric patients based on the review of literature. First, I will present published clinical studies in children followed by reported adverse events from case reports. I will also briefly present guidelines and policy statements from two healthcare professional organizations, then the overall summary.

Published clinical studies in children what do we have? The literature search resulted in 11 public clinical studies involving children in the last 50 years. It will be noted that studies in children are few and sparse. There were four studies published from 1951 to 1966, one from the '80s and six from 1990 to 2004 to the present. Cough was the most frequently studied symptom. Some studies are better than others and none of the studies reported deaths or serious adverse events.

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Later, I will present a tabulated summary of these studies.

(Slide)

DR. LOPEZ: These are the active ingredients included in the clinical studies. The ones highlighted and those with the asterisk, if you have a black and white copy, are the common active ingredients found in the currently marketed OTC cough and cold products in children. Analgesics will not be discussed in this presentation.

(Slide)

DR. LOPEZ: These were the studies published from 1951 to 1966. This included children 2 months to 16 years of age. There was no placebo arm in two of the studies.

On the last column are the author's conclusions on efficacy. There are two studies on antihistamines. One evaluated common cold systems and the other evaluated nasal allergies symptoms. One study was on decongestants, two were on combination products wherein one evaluated cough only and another evaluated cough and cold symptoms.

(Slide)

DR. LOPEZ: These were the studies published from

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1990 to 2004. These included children 1 months to 18 years old. On the last column are the author's conclusions on efficacy. The indication evaluated was cough and cold symptoms. There were two studies on antihistamines, three on antitussives and one on combination products. It is to be noted that these studies have several limitations.

In the next slides will present a list of some of these limitations and some of the challenges for future studies in children. The best way to describe some of these studies is by citing examples. First, in some studies symptoms evaluated where not related to the expected therapeutic effect of the drug, such as appetite or decreasing appetite, crankiness, fever and also parental sleep is not listed as an indication in any of the drugs.

(Laughter)

DR. LOPEZ: That's good. That means you're listening. Second, in most studies outcome measures were not precise or well defined, for example, in assessing frequency of cough very much versus a lot or a little versus occasional are difficult to distinguish from each

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other. In addition, cough is an objective outcome to measure. One study actually measured cough frequency by using a tape recorder. This or another form of cough-counting technique would be very useful in measuring the efficacy or the frequency of cough. Third, treatment outcomes were not measured at the time expected efficacy of the drug. For example, evaluating symptoms after 24 to 48 hours may be too long and this could affect efficacy assessment.

There was one study where symptoms were assessed two hours after drug administration and this may be more

appropriate as treatment effect may occur within this time period.

Fourth, symptoms were not frequently measured. For example, assessment of symptoms more than once a day may be necessary in assessing the efficacy of a drug and fifth, inadequate dosing, including amount and frequency, to elicit the effect of the drug. For example, for a drug given overnight, two doses may be necessary in a span of eight to ten hours sleeping time.

(Slide)

DR. LOPEZ: The following is an additional list.

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Some of the studies were conducted at least 50 years ago and therefore were done under a different standard. There was no placebo arm in two of the studies claiming efficacy, randomization or blinding was not mentioned or clear in some of the studies and it is not clear if the studies were adequately powered to show a difference between drug and placebo and concomitant use of other medications such as antibiotics. These limitations are also among the challenges encountered for any efficacy study that will be conducted in children.

There are several challenges in conducting clinical studies evaluating symptoms of cough and cold in children. The following are some of these: symptoms from the common cold are believed to be self-limiting and peak within a few days after infection. In other words, it gets better over time. Unlike cough, symptoms such as nasal congestion and rhinorreha are subjective outcome measures and may be difficult to assess.

Young children are difficult to study because children are less verbal or are unable to express their symptoms well. One has to rely on caregivers for assessment of symptoms.

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I will now move on and present adverse events from published case reports. There were seven articles presenting adverse events from case reports. A total of 32 cases were reported, 80 percent or 26 were in less than 16 months old. The majority has limited clinical information. In one article, eight out of ten had obvious underlying causes of death such as sepsis and compressional asphyxia.

It is not possible to discuss all these cases. Therefore, to give you an idea of what cases are out there, I picked three cases in which patients had cough and cold symptoms or were given cough and cold medicines, had detectable or increased blood levels of cough and cold medicines or death was reported to be due to these medications. The first case is a 9-month old male with persistent crying, fever, non-consolable for a week, no week for three nights, cough for several weeks, no rhinorreha and (inaudible) three times a day, no diarrhea. Mother reported giving ibuprofen. There was no mention of other meds in the history.

These were the vital signs at the emergency room. He was evaluated for meningitis -- CBC and CSF were

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normal. Several hours later he was alert, active, playful and tolerating oral fluids. He was given iron antibiotics and was discharged to follow up the next day. Twelve hours later he was in cardiopulmonary arrest and was pronounced dead. The autopsy showed no gross abnormality. Postmortem urine toxicology testing was positive acetaminophen, pseudophedrine and chlorpeniramine, dextromethorphan and phenolprophenalmine. Note that from the history, ibuprofen was the only medication mentioned.

Here are the patient's postmortem drug levels in the blood. Note again that toxic data on toxic levels on children are limited for most cough and cold medicines. As we have heard postmortem drug redistribution could increase levels up to three times. On the second column, you will note that the pseudophedrine level was at least 20 times higher than the expected blood concentration at therapeutic doses in adults.

It is assumed that levels in children are comparable to adults. The dextramethorphan and phenylpropanol levels were elevated as well to at least three times the expected level. The cause of death was listed as mixed drug intoxication unintentional. Further investigation

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revealed that numerous OTC cough and cold preparations were given by caretakers, but not intentional. In this case it appears that parents were not aware the preparations with multiple active ingredients were being given at the same time.

The next case was reported from a coroner's office. There was limited clinical information provided. This was a 5-month-old infant with a history of ear infections and congestion, given antibiotics and a known OTC cold medicine containing dextramethorphan. And after taking OTC meds, took a nap on his belly and three hours later was found unresponsive and died. The autopsy showed ear fluid and congested lungs.

The cause of death was listed as acute multiple drug intoxication. Toxicology findings revealed the following in the blood: pseudophedrine, dextramethorphan, ephedrine, acetaminophen, carbonoxamine and metachlopheniramine. Note that these drugs levels include both RX and OTC products. Further investigation revealed that the older siblings were routinely given OTC medications to sedate them.

The last case was reported by a medical examiner.

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This is a 2-month-old with cold symptoms, crying until 2:00 in the morning. Mother fed infant with water and small amount of acetaminophen. Infant fell asleep. Infant woke up and later was placed in prong position with head to side, later was found unresponsive and pronounced dead in the emergency room.

At the scene were two bottles. One containing a small amount of formula and one containing pink tinted liquid. The following medications were received by the medical examiner -- infant pain reliever, suspension drugs, and children's pain reliever, cough formula containing dextromethorphan. This is the infant's toxicology result. Again, note that data on toxic levels for these medications are limited in children. On the last column you will note that the pseudophedrine level was at least 28 times more than the expected blood level at therapeutic doses in adults. For brompheniramine, it was at least 18 times more.

We do not know how much medications were taken by the child. However, on the last row of this table, note that the amount left on the baby bottle containing pink fluid was much more than what a 2 or 5 year-old child

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should have had. It appears that caregivers do not follow instructions on the label and administer the medications

through the baby bottle instead of using a dropper, which would have delivered a much smaller amount.

For an infant this young, the label instructs parents to consult a physician. It is not clear if this was done. This child had an overdose of these medications based on blood levels.

In summary, adverse events from case reports have one or two of the following in common. Most deaths had detectable or increased blood levels of these medications, mostly pseudophedrine. Data on toxic levels in children are limited for most drugs and therefore postmortem levels are difficult to interpret. In cases where drug level were excessively elevated, the contribution of cough and cold medicines to the death or serious adverse event should be suspected despite confounding factors. Most deaths or serious adverse events were confounded or had limited clinical information.

Deaths could have been due to other conditions such as Sudden Infant Death Syndrome or child abuse and that administration of cough and cold medicines was

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coincidental. Overdose was mostly due to medication error. For most cases there is no information if a physician was consulted in children less than 2-years-old as stated in the label.

In the next slides, I will briefly present the guidelines and policy statements from two healthcare organizations.

(Slide)

DR. LOPEZ: The American Academy of Pediatrics has issued a policy statement on the use of codeine and dextromethorphan containing cough remedies in children and it stated "There are no well-controlled, scientific studies to support efficacy and safety of narcotics or dextromethorphan as antitussives in children. Suppression of cough in many pulmonary diseases may be czardas (phonetic). Dosage guidelines are extrapolated from adults and thus, imprecise for children. Further research and dosage, safety and efficacy are needed. Education of parents about the lack of proven effects and the potential risks of these products is needed.

If you go to the APA website under "Parenting Corner," it states "Never use cough and cold preparations

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in a child under 3 years of age unless prescribed by a pediatrician." The AAP has recently sent a letter expressing their opinion on these medications and it is in your background package.

The American College of Chest Physicians published guidelines for evaluating chronic cough in pediatrics and one of the recommendations relates to the OTC medications and it states, "In children with cough, cough suppressants and other OTC cough medicines should not be used, especially young children may experience significant morbidity and mortality."

In summary, published clinical studies in children did not establish efficacy of cough and cold medicines when used to treat symptoms of the common cold, including cough. However, there were deficiencies -- it is important to note that there were deficiencies in the design of these studies, such as definition and timing of treatment outcomes, inadequate dose, including amount and frequency and studies may not have been adequately powered to show a difference between drug and placebo.

There are no serious adverse events or deaths from all published, clinical studies reviewed involving

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children. There were cases in which it was obvious that excessive levels of medicines in the blood from patients in the case reports who died or had serious adverse events were mostly due to dosing and/or administration errors by caregivers. In many cases it is difficult to determine the exact contribution of these medications to the deaths or serious adverse events. Thank you. And you will now here from the next speaker.

DR. AKHAVAN-TOYSEKANI: My name is Gita Akhavan-Toysekani. I'm a safety evaluator with the Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology and I will be presenting the reviews of reported adverse events and poisonings associated with cough/cold products in children under 6 years of age.

The outline of the presentation is as follows. I will go over the objectives, then I will present the data from the two databases that we reviewed. The first database that we looked at was the adverse event reporting system, which from hereon I will refer to, as AERS and I

will give a brief background to spontaneous adverse event reporting. I will present the first AERS review, which was completed in February 2007 and looked at fatalities in

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children 6 years of age and under followed by the second AERS review, which was completed in September 2007 and was an expansion of the first review to all serious adverse events in children under 6 years of age. Therefore, some of the cases may be overlapping between the two reviews.

In addition to the AERS data, I will present the data from the Toxic Exposure Surveillance System, which is a national database of the National Association of Poison Control Centers. There might also be an overlap of cases between the two databases. I will provide a summary of the overall findings and finally provide some points to consider.

So the objectives of this presentation are to present AERS cases of serious adverse events, including deaths associated with cough/cold medications in children under 6 years of age, to discuss the contribution of drug overdose to serious adverse events and death to show that most adverse event cases were reported in age groups where there are no dosing recommendations on the OTC product label, to discuss the association of single versus multiple ingredients and also to discuss the association of prescription versus OTC cough/cold products to serious

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adverse events and finally, to review overdose and poisoning exposure cases and association with cough/cold products reported to the American Association of Poison Control Centers.

Before going into the AERS reviews, I would like to provide a brief background to spontaneous adverse event reporting. It is a voluntary system for consumers and healthcare professionals to report adverse events. Under the Code of Federal Regulations, sponsors of an approved NDA product are required to report adverse events. These reports are sent to the agency through the FDA Med Watch Program and stored in the AERS database, which currently contains over 3 million reports of adverse events.

Spontaneous adverse events reporting are useful since it includes all U.S. marketed products. It is best to detect events not seen the clinical trials and is a

good tool for events with rare background rates and short latency. There are some limitations to spontaneous adverse event reporting, such as extensive under reporting. In particular, 40 OTC monograph products, there have been no prior reporting requirements. However, new legislation requires reporting that will begin on

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December 22nd of this year.

Also, the quality of reports may be variable. Other factors affecting reporting of adverse events may be reporting biases based on variety, media attention a particular product is receiving or if it's a new drug. The actual numerator, which is the number of events in a population, and a denominator, which is the number of patients exposed, is not known and so the quantification of risk assessment is subject to limitations.

Also, causality of drug is often in question. For the safety review of cough and cold products, one major limitation is that these products are commonly in combination, therefore, a clear drug event association is difficult to establish.

I would like to highlight the findings of the first PERS review for pediatric deaths, which is included in your background package. In this review, the AERS database was searched for fatalities in children 6 years of age and under between 1969 and September 2006. The cases were limited to U.S. only and included single and combination as well as prescription and OTC products. Since these cases involve combination products, there may

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be some overlap of the cases among the different drug groups.

These cases were associated with the following drugs, the three decongestants, pseudophedrine, phenylephrine, ephedrine and the three antihistamines, diphenhydramine, brompheniramine and chlorpheniramine. For the decongestants, the number of domestic cases with a death outcome was as follows. For pseudophedrine there were 46 cases, four for phenalephrin and four for ephedrine. Among the decongestants a majority of the cases reported in children under 2 years of age. Drug overdose was a common reported adverse event and accounted for about 72 percent of all cases.

These cases were associated with both prescription and OTC cough/cold products and the majority of the cases or 24 out of the 28 cases with the reported postmortem level were above the adult therapeutic level. I would like to point out that there are limitations to accurately interpreting postmortem levels, especially considering its potential for postmortem redistribution, as was discussed by Dr. Roy. Therefore, the reported drug levels cannot be used as a definitive data in attempting to predict at

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mortem concentrations, but rather a support for clinical findings.

Across the top are the three decongestants and going down there are the number of cases associated with a drug overdose and the reported causes of death in this review. I would like to draw your attention to two points. Overdoses were common adverse events reported in these cases and the manner of overdose included use of multiple cold/cough products, medication errors, accidental exposures and intentional exposures. Drug intoxication or overdose was one of the causes of death reported across all three decongestants.

For antihistamines, the number of domestic cases with a death outcome was as follows. For diphenhydramine there were 33 cases, 9 for brompheiramine and 27 for chlorpheniramine. The majority of the fatal cases were reported in children under 2 years of age. Drug overdose was a commonly reported adverse event in these cases and accounted for about 65 percent. In cases were the product classification was known, these cases were associated with both prescription and OTC cough/cold products in about 64 percent or 18 of the 28 cases where the reported

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postmortem level were above the adult therapeutic level.

Similarly, as with the decongestants, overdose was commonly reported in these cases with drug intoxication or overdose as one of the reported cause of death across all three antihistamines.

Now, I would like to present the second AERS review, which was an expansion of the first one and looked at all serious adverse events. Serious, by regulatory definition, includes outcomes of death, hospitalization, life threatening, requiring intervention, disability,

congenital anomaly and others. Because this review includes death, there may be overlapping cases from the first review.

The AERS database was searched for serious adverse events in children under 6 years of age between January 2002 and May 2007. The last five years were selected to focus on the most relevant cases as the cough and cold preparations have been reformulated over the years.

Again, similarly to the first review, we limited the search to U.S. only and included single and combination as well as prescription and OTC products. The four drugs were pseudophedrine; dextromethorphan, chlorpheniramine

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and diphenhydramine were selected since they represented the highest number of adverse event reports in the AERS database for the OTC cough and cold products.

(Slide)

DR. AKHAVAN-TOYSERKANO: This slide represents the demographics and across the top are the four drugs. The median age for the four drugs range from 18 months to 24 months. The majority of the cases for pseudophedrine and dextramethorphan, which are in the second and third column, were reported in children under 2 years of age and for antihistamine products the majority of the cases were in the 2 to 5 year age group. Males represented a higher percentage across all four drugs.

(Slide)

DR. AKHAVAN-TOYSERKANO: This slide shows the dose and time to onset for the four drugs. The dose was reported in approximately half of the cases for pseudophedrine, dextromethorphan and chlorpheniramine. The median dose did not exceed the recommended dosage for the lowest age group, whereas for diphenhydramine, the median dose did exceed the recommended dosage for the lowest age group. Time to onset was also reported in

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about half of the cases with a median time to onset of one dose across all four drugs.

(Slide)

DR. AKHAVAN-TOYSERKANO: This slide shows the breakdown of product classification. A majority of the cases in this review were associated with an OTC product. With the exception of diphenhydramine, most cases were

associated with a combination or multi-ingredient product. Approximately 40 to 50 percent of the cases were coded for drug overdose. These cases were further evaluated for the manner of overdose and approximately 12 to 32 cases were associated with an accidental exposure, 2 to 11 cases reported an intentional overdose by parent or caregiver, 4 to 13 cases reported a medication error and in about 4 to 27 of the cases the manner of overdose could not be determined.

The focus of the review was adverse events related to cardiac, nervous system and respiratory disorders. Adverse event terms related to nervous system disorders were most frequently reported with all four drugs. In particular, convulsions and depressed level of consciousness were commonly noted. We further evaluated

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the adverse events to see how many occurred in the context of a drug overdose for each of the drugs.

You can see that most of the adverse events occurred in the context of a drug overdose with the exception of convulsions. The majority of the convulsion cases did not report a drug overdose.

We also looked at the four types of adverse events by age groups. The majority of the cases associated with a cardiac and respiratory disorder, which are on the far ends, occurred in children under 2 years of age. Depressed level of consciousness occurred fairly evenly between both age groups while the convulsion cases appear to occur slightly more in children 2 to 5 years of age.

We also looked at hallucinations associated with the four drugs. In children under 2 years of age, there was one report of hallucination associated with each ingredient. Since there is no dosing information in children less than 2, we cannot determine if the doses were within the therapeutic range. In children 2 to 5 years of age, we further looked at cases reporting dose as equal or less than the therapeutic dose and above the therapeutic dose.

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For pseudophedrine, dextromethorphan and chlorpheniramine, there were mostly reported within or below the therapeutic dose, whereas for diphenhydramine, they reported more frequently in cases where the dose

exceeded the therapeutic dose. Time to onset ranged from one dose to three days. Approximately half of the cases reported visual hallucinations.

The description of the visual hallucinations included seeing bubbles, snakes, and frogs, big creature, snakes, spiders and scorpions, imaginary things and in one case the patient reported bugs everywhere, balls were coming after her and raining in her room.

In this review cases with a death outcome were reported in about 30 percent of the cases. We also looked at postmortem blood levels for pseudophedrine, chlorpheniramine and diphenhydramine the median postmortem blood level was above the adult therapeutic levels, and for dextromethorphan it was within the adult therapeutic level.

I would like to present the few cases from the review. The first case involved a 2-month-old infant who was administered PediaCare infant decongestant and cough

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concentrated drops as recommended by a pharmacist for an unknown indication. Past medical history and concomitant meds were unknown. One hour after receiving a single dose of .4 mls, which equivalent to 3.75 milligrams of pseudophedrine and 1.25 milligrams of dextramethorphan, the infant experienced a heart rate of 240 beats per minute and was hospitalized.

The infant was given unspecified medications to slow the heart rate. She was also treated with an unspecified antibiotic. It was reported that all adverse events had resolved and the infant was released from the hospital after seven days. I would like to point out that the label provides dosing for down to 2 years of age and there is no dosing recommendation for under 2. However, the dose that was administered in this case is a quarter of what a 2 to 5 year-old would receive.

The second case involved a 2-week old infant who was given an unspecified amount of infant PediaCare decongestant, which contained pseudophedrine, for congestion as recommended by a physician. There was no reported past medical history or concurrent medications. Immediately after the first dose, the patient experienced

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cardiac failure and super ventricular tachyacardia. They

patient was treated with doxylamine and unspecified medication in the hospital and discharged after two weeks with the events resolved.

A third case involved a 5-year-old female who received Triaminic cough and sore throat for cough. The patient received one dose or 5 ml, which includes 15 milligrams of pseudophedrine, 5 milligrams of dextramethorphan and 160 milligrams of acetaminophen. The patient experienced seizures the next morning. The patient was evaluated by a physician and it was reported that all vitals were fine. Outcomes and interventions were unknown. However, it was reported that the patient experienced the same adverse event with the same medication two years prior.

In summary of the AERS review of serious adverse events in children, over 50 percent of the cases associated with pseudophedrine and dextromethorphan occurred in children under 2 years of age. Over 50 percent of the cases associated with chlorpheniramine and diphenylamine occurred in children 2 to 5 years of age. Cases were associated with both prescription and OTC cough

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and cold products. However, the majority were OTC products. Over 75 percent of the cases associated with psuedophedrine, chlorpeniramine and dextromethorphan involved a multi-ingredient cough and cold product.

Approximately 30 percent of the cases reported death outcome, overdose was reported in about 48 percent of the cases. Among all cases, approximately 22 percent were accidental exposures, 6 percent were intentional overdoses by parent or caregiver, 9 percent were medication errors and in about 11 percent of the cases the manner of overdose could not be determined. Serious adverse events related to the cardiac, nervous and respiratory systems have been reported, both in the setting of overdoses and outside of overdoses.

Convulsions have been reported more commonly outside of overdose and appear slightly higher in children 2 to 5 years of age, whereas serious cardiac and respiratory events have been reported mostly in the setting of a drug overdose.

Now, I would like to present data from the Toxic Exposure Surveillance System, which more recently is known

as the National Poisoning Data System. This review was a high-level analysis undertaken to estimate the burden of adverse reactions and poisonings attributed to cough and cold preparations, including diphenhydramine in young children tests the poisoning database of American Association of Poison Control Centers, which contains over 41 million human poison exposure cases. We reviewed annual reports from 2001 to 2005 and included only cases that listed cough/cold preparations or diphenhydramine as a primary agent. One caveat similar to spontaneous adverse event reporting is that there is extensive under reporting.

For the cough and cold products in children under 6 years of age, the total number of cases increased slightly from about 60,000 in 2001 to about 70,000 in 2005. The overall percentage of cases involving children under 6 years remains constant at about 61 to 62 percent in the five-year review period. For all ages, a majority of these cases resulted from an unintentional exposure, about a quarter were treated in a healthcare facility.

For the diphenhydramine products in children under 6 years of age, the total number of cases increased very slight from 13,044 in 2001 to 13,445 in 2005. The overall percentage of cases involving children under 6 years remained constant at about 43 to 46 percent. For all ages, 45 to 75 percent of diphenhydramine cases resulted from unintentional exposure and about 42 percent of those required treatment in a healthcare facility.

In children under 6 years of age, 14 fatalities were reported in association with cough/cold and diphenhydramine products in a five-year review period. The age range from 2 months to 5 years, the majority of deaths occurred in children 12 months or younger, three fatalities were noted in association with the use of single ingredient cough/cold or diphenhydramine product and 11 fatalities were noted combination products or use of multiple products.

In summary, data from poison control centers suggest substantial number of overdose and poisonings in association with cough/cold and diphenhydramine products, both OTC and prescription products were involved.

Children under 6 years of age make up 40 to 60 percent of all poisoning cases in association with cough/cold and diphenhydramine products.

Based on the two AERS reviews and the test review,

our overall findings were that the use of OTC and prescription cough/cold medications in children under 6 years of age has been associated with serious adverse events, including death. Drug overdoses commonly contributed to serious adverse events and death. The manner of overdose was identified as accidental exposure, intentional overdose and medication errors, which Dr. Abate will discuss in more detail.

Most occur in age groups where there are no dosing recommendations on the OTC product label. The product label states to consult a physician for less than 2 years of age for decongestants and antitussives and less than 6 years of age for antihistamines. However, there is no information on how much can be given. Most cases involved multi-ingredient cough/cold products and data from poison control centers suggest a substantial number of overdose and poisonings in association with cough/cold and diphenhydramine products.

We would like you to consider an educational campaign directed toward healthcare providers and parents about the use of cough and cold products. The labeling of cough/cold products should include prominent language to

describe the risk of overdose in children. Labels should indicate that cough/cold products are not recommended in children under 2 years of age.

And finally, consideration should be given to having only single ingredient cough/cold products for pediatric formulations. Thank you.

DR. ABATE: Good afternoon. My name is Rick Abate. I'm a safety evaluator in the Division of Medication Errors and Technical Support in the Office of Surveillance and Epidemiology. I'm here to describe how medication errors are impacting the safe use of over-the-counter cough and cold products in children under 6 years of age.

I'm going to begin with a selection of medication errors involving over-the-counter cough and cold products used in children under 6 years of age from our AERS

database. I'll discuss the factors contributing to the medication errors and finish with some points to consider.

(Slide)

DR. ABATE: Most of us have been to the cough and cold section in a pharmacy and this is pretty much what it looks like. The slide shows the wide assortment of products a consumer has to choose from and it is easy to

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see, by looking at the number of products available, how a parent can be overwhelmed. Therefore, it is not surprising that a number of medication errors reported to the agency actually occur in this selection stage in the pharmacy.

However, it is important to note that OTC medication errors are infrequently captured through spontaneous reporting mechanism for many reasons, not the least of which is consumers not being aware that an error has occurred. For today's presentation we have selected four cases from our AERS database that illustrate just some of the issues that are impacting the safe use of cough and cold products in children under 6. The first case involves product selection error within a brand, the second case involves duplicate therapy, the third involves confusing nomenclature and the fourth and final case involves improper dosing.

Before going into the details of each case, I would first like to discuss the difficulties consumers face when selecting a product within a brand. During this presentation you will hear specific product names in the cases and you may see images in our slides. These images

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and names are simply to illustrate the challenges parents face using cough and cold products. It is not my intention to single out a single, particular brand since our analysis of the medication errors did not find any one brand to be more problematic than another.

(Slide)

DR. ABATE: This slide illustrates just one of the brands available in the marketplace. As you can see, this company markets a total of eight pediatric cough and cold formulations within their brand. Looking across the top of this chart, you can see that even when a parent knows the brand name of the product they are seeking or that a

prescriber has recommended, there is an opportunity for the parent to select the wrong product because they have so many similar products to choose from.

Looking to the left-hand column of the chart, you see that the sponsor guides the product selection by emphasizing the symptoms the product is intended to treat rather than distinguishing the product by the active ingredients. This chart is not like many other manufacturers methods of differentiating products. It is important to note that although many of these treat the

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same symptoms they may or may not contain different active ingredients.

As an example, I draw your attention to these two products from the previous chart, cold and cough and long-acting cough plus cold. These products have similar names, yet they differ in one symptom relieves stuffy nose and the active ingredient content is different. The cold and cough product contains phenylephrine, brompheniramine and dextromethorphan. While the product called "long-acting cough plus cold" contains a different antihistamine, chlorpheniramine and a higher concentration of dextramethorphan.

Later in this presentation, I will highlight why the name may be a contributing factor in an error. This first AERS case illustrates the type of selection error that can occur within a brand. A physician verbally recommended that a 19-month-old receive three quarters of a teaspoon of the children's cold product on the left. The family went to the store and found the brand that was recommended, but selected the wrong product within the brand. They selected infant drops on the right.

The product on the right does not contain

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brompheniramine and has three times the concentration of pseudophedrine. The parents gave the child three quarters of a teaspoon of the infant drops, which resulted in a threefold pseudophedrine overdose.

In our analysis, we identified several factors that may have contributed to this error. First, both of these products within the brand have similar nomenclature. They both use children's Dimetapp to describe the product. The trade dress, meaning the look, layout of the label and the

color the manufacturer uses for a specific brand is similar in both products. There may also have been a lack of knowledge on the part of the caregiver who could have overlooked, ignored or failed to understand the information presented in the drug facts label.

Also, you'll see that the product the parents selected, like many other products marketed for the pediatric age group, include an image of an infant, baby or small child on the principal display panel of the carton. Because this case involved a 19-month-old child, it is possible that this image may have fostered the mistaken belief that the infant formula was the product the prescriber had intended.

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Our second AERS case describes duplicate therapy. Duplicate therapy can occur when parents or caregivers unknowingly administer the same active ingredient or same class of ingredients to their child from different products. In this case, the parent used two products, both containing pseudophedrine.

A 6-month-old who was diagnosed with pneumonia was prescribed amoxicillin along with corboxifed RF, an unapproved product that contain pseudophedrine and carbonoximine. The prescriber recommended the parents purchase plain Tylenol or Motrin for the fever. However, the parent mistakenly purchased infants Tylenol cold, a product that contained pseudophedrine and acetaminophen. Both pseudophedrine-containing medications were given for a day and a half. The mother stated that she dosed the infant's Tylenol cold according to the instructions on the box. This is a monograph product that has no dosing on the label for patients under 2 years of age. Therefore, the source of dosing extrapolation in this case is unclear.

The Coboxifed (phonetic) was administered every four hours rather than four times a day. This 6-month-old died

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and although the causality cannot be definitive linked to the error or to the individual active ingredients, it was noted in the report that the child received a total pseudophedrine dose of 200 milligrams over 36 hours. To put this in perspective, the maximum-labeled adult dose of pseudophedrine is 240 milligrams in 24 hours.

When examining the factors contributing to the overdose and selection error in this case, we again noted that the products names are very similar, Infants Tylenol Cold versus Infants Tylenol and that both use a similar red color scheme. Because Tylenol Cold is not labeled for this age group, the drug facts label would lack sufficient detail for the mother to dose the medicine appropriately.

Moving back to the Coboxifed label, prescription pharmacy labels are space restricted on the amount of text they can display, and as a result multi-ingredient prescription products tend to display only the trade name and not the individual active ingredients. Therefore, in this case it is possible or probably that the consumer may not have been aware, from looking at the prescription label that the product contained pseudophedrine. In addition, the mother misunderstood the direction of use

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for the prescription Coboxifed. Collectively, these factors resulted in this overdose.

Now, we're going to move from duplicate therapy to discuss another challenge parents and caregivers face when selecting cough and cold medications. Because these medications are used to treat symptoms, the emphasis of the symptoms on the carton may lead the parent to rely on that information rather than the drug facts when selecting the products.

(Slide)

DR. ABATE: This slide shows just a sample of cough and cold products available in the market today. The vast majority of cough and cold products contain multiple active ingredients. And because the active ingredients can be used to relieve a variety of symptoms, manufacturers often select trade names that reflect the symptoms the product is intended to relieve.

From this sample, you can see highlighted in pink that 9 out of 12 names contain the word "cold" and highlighted in green, 8 out of 12 contain the word "cough." Also, the names typically include the manufacturer's given brand name such as PediaCare or

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Robitussin, along with other qualifying statements such as daytime, nighttime and long acting.

There are several aspects of this nomenclature that

can cause confusion. These products may not contain the same active ingredients to treat the same symptoms or they may contain the same active ingredients to treat different symptoms. In addition, a parent may misinterpret the symptoms on the principal display panel or may focus on a single symptom in the name and overlook the other active ingredients.

Case Three will illustrate just that. A 4-year-old developed a fever with no other cold symptoms. But to threat this fever, the parents purchased Triaminic Severe Cold and Fever. While this product contained acetaminophen to treat the fever, the parents failed to realize that it also contained three additional and unnecessary active ingredients pseudophedrine, dextramethorphan and chlorpheniramine. Although the product was labeled to administer every four hours, the parents administered the product every two and a half to three hours for an unknown number of doses until the child began to seize.

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The child was treated in the hospital for tachycardia and seizure and the final outcome in this case was not reported. Although these events were not definitively linked in the case to the medication error, it is plausible that the error had a role in these events.

The product nomenclature was a contributing factor in this error because the parents focused on a single symptom in the name, "fever," rather than the drug facts label and the parents may have overlooked or deliberately ignored the label dosing frequency because they wanted to quickly reduce the fever or they could not understand the directions on the label. The parents may have had inaccurate perception of risks and thought the other active ingredients could not be harmful to the child.

So now we're going to shift from the errors that occur when selecting the products to the challenges parents face using cough and cold products safely in their home. Improper dosing is a common type of error in this setting.

Doses devices have a critical role in the safe use of cough and cold products in pediatric patients because the majority of the products marketed for these

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populations are liquid formulations. These liquids are generally available in bulk bottles and require individual doses to be measured at the time of use. Dosage devices include cups, droppers, oral syringes and the like.

These devices may or may not be packaged with the medication. The intent of these devices is to deliver an accurate amount of medication to the patient. As such, measurements should agree with the doses provided by the product labeling and be presented in a manner that minimizes confusion.

Well-designed, dose-specific devices are associated with accurate dosing of medicines, while poorly designed or no device can lead to inaccurate doses of medicine. This is supported by post-marketing surveillance in a study by McMahon and Associates published in Pediatrics in 1997. The next few slides will illustrate some aspects of poorly designed dosage devices.

(Slides)

DR. ABATE: Here is a device that contains multiple units of measure, including mls, cc, tablespoons, teaspoons, dessertspoon, drams and fluid ounces. While covering all the bases may seem safer, more choices

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actually increases the potential for error as parents confuse the various units of measure the child is supposed to receive. Additionally, this cup is clear with clear embossed lettering that can be difficult to read.

Here is another poorly designed dosing cup. While this one displays just two units of measure tablespoons and teaspoons the product labeling only expresses the dose in teaspoons. Adding to our concern, we know from post-marketing surveillance that these units of measure are often confused with one another and have resulted in case of threefold over and under doses.

Here is another dosing device that uses the correct unit of measurement, but lacks the half a teaspoon graduation, even though the product labeling allows for doses of a half a teaspoon in younger children. So a parent would have to estimate the one-half teaspoon doses using this device.

We also see medication errors arise when the device provided with the product is not what the prescriber had expected or envisioned when dosing their pediatric

patients. In this case the prescriber recommended a dose of one and a half dropper's full of a cough/cold product

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for a 1-year-old because this is the device he was most familiar.

The mother purchased the correct product, but found an oral syringe in the package. She mistakenly thought the oral syringe was the dropper the prescriber had referred to and dosed her child using one and a half syringes, which delivered twice the recommended volume and resulted in a twofold overdose. This error occurred even though the dose instructions printed in the drug facts are specific for the oral syringe included in the product.

This case has a number of contributing factors. First, this product is called a drop, but is not dosed by a dropper and the prescriber was not aware that this particular drops formula was packaged with an oral syringe. As a result, the prescriber provided dosing recommendations that conflicted with the drug facts label, leaving the parent to reconcile the difference.

The parent was probably not aware that the oral syringe packaged with the product was not what the prescriber had referred to when dosing the child. Conceptually, a parent may not be aware that these devices may measure significantly different volumes.

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Collectively, these factors resulted in an overdose.

Even if the product contained a dropper, a dosing error may not have been avoided as post-marketing surveillance and the literature indicates the droppers are difficult to manipulate and parents frequently are unable to measure medicines accurately.

In summary, medication errors do impact the safe use of cough and cold products of children under children under 6 years of age, particularly, when selecting and dosing these products. There are several areas that can improve upon to better ensure the safe use of over-the-counter cough and cold products in children. Based on the risks we have identified, my division offers the following points for the advisory committee's consideration.

Similar to the previous presentation, limiting cough and cold formulations for us in the pediatric population

under 6 years to a single active ingredient may help to reduce the risk of medication error and harmful outcomes related to duplicate therapy and product selection errors. Given the risk of medication errors involving the improper dosing of liquid cough and cold medications,

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please consider whether there should be a requirement for manufacturers of these products to provide well designed and product-specific dosing devices for these liquid medications.

Additionally, many of the dosing errors involve the use of cough and cold products in patients younger than the minimum age listed in the drugs facts label. Please consider whether further study should be requested to develop more comprehensive dosing instructions that can be provided to consumers on the drugs facts label to help avoid parent dose extrapolation.

Also, please consider if the "consult your physician" statement should be revised to more explicitly convey the risks associated with cough and cold medication use in unlabeled patient populations to more effectively promote communication between consumers and prescibers. However, even with this modification, the errors may not be entirely avoided since many of the medication errors we've discussed today involved communication with the physician prior to use.

And finally, given the role that lack of knowledge has on impacting the safe use of over-the-counter cough

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and cold products, please consider educational campaigns directed at healthcare practitioners and consumers to help improve the safe use of these products. We appreciate the Committee's guidance and opinion on the merits of each of these points. Thank you.

DR. TINETTI: Thank all the presentations by the FDA. It was very helpful. I think what we're going to do now is we'll have about half an hour or so of questions to the speakers, then we'll have a short break. And the questions now can be for any of the speakers.

I think if there were people we didn't get to this morning, so I'm going to ask if any of Drs. Rosenthal, Atkinson or Hennessy still had the questions for this morning? Did you still have your question, Dr. Atkinson?

Okay. We'll take those first and then we'll take any additional questions.

DR. ATKINSON: Yes, my question was for the president of the Maryland Chapter, Dr. Levy if he's still here. Okay. All right. Maybe someone from that group might know, but he had some very deeply held beliefs about which were supported by data that was presented about the ineffectiveness of cough and cold medicines. I wonder

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if there's any if a general poll has been done in the Maryland chapter of the AAP or if the AAP has polled its members and gotten a general opinion from the practitioners about what their thoughts are about this issue?

DR. SHARFSTEIN: I can ask him that question and see if I could get the Committee the answer by tomorrow. I will say that when he signed the petition he signed on behalf of the chapter, the academy, and that involved consultation with the members because I know it was discussed subsequent to their meeting. So officially, the chapter actually was a signatory to the petition.

DR. ROSENTHAL: Jeff Rosenthal. My question is also to the petitioners from this morning. I'm wondering if the recommendations that are in the petition are adopted, if you can help us to anticipate some of the negative and unanticipated consequences of adopting those recommendations. In other words, do you think that antibiotics will be prescribed more or other unanticipated changes in practice will occur that we should consider?

DR. SHARFSTEIN: I'm sorry, sir. I don't know if I can anticipate the unanticipated things. I think that's a

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good question. I think we know because the under 2 population a lot of those products were taken off the market last week and the sky didn't fall down. But at least in the immediate range, it's not like a panic would ensue. I think that's pretty unlikely.

That's pretty much, I guess I could say based on the experience we've had in the last week, and I'm not aware of any I don't know whether Dr. Snodgrass is of discussion, particularly, around the question of antibiotics. I think the pediatricians have been making progress on the question of inappropriate prescription of

antibiotics.

DR. TINETTI: Do you have any further comment on that? I think that's an important question.

DR. SNODGRASS: The only thing I could think of, with regard to antibiotics, those are prescription products. So they would have to see a physician so that might be a bit of a gate keeping for that particular possible unanticipated consequence. Obviously, further education about the appropriateness of prescribing or not would be indicated.

DR. TINETTI: Dr. Dure had a hand up.

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DR. DURE: Yes, I'd sort of turn Dr. Rosenthal's question over to the industry representatives. Do you have any objective data that points to the benefit of the cough and cold preparations? And I don't really know I'm not interested in opinion. Do you have any objective data about the benefit of these drugs?

DR. SUYDAM: I think Dr. Walson might be able to answer that question best, if I could ask Dr. Walson to come to the microphone.

DR. WALSON: I think that in the briefing book the data on healthcare costs was included. Is that the kind of data

DR. DURE: Are you referring to the Teaman (phonetic) article and the 110,000 visits over 14 years?

DR. WALSON: Yes, basically. Actually, I'm not sure it's that article, but there was a review of various articles done. The other answer to the question really is not as a member of not as somebody representing industry. Obviously, I don't work I'm not in industry, but as a board member of the Alliance for the Prudence Use of Antibiotics, which is a non-profit organization trying to prevent inappropriate use of antibiotics, I can tell you

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that one of the things we one of the ways we've been able to cut down on antibiotic use, which as mentioned, we are finally making some progress, is by recommending OTC product use.

So I don't have data, but I can tell you that it will impact what we've been trying to do to get people who we know overuse antibiotics. I think there are a lot of data. I'm sorry I don't have the data with me on how much

inappropriate antibiotic use there is, but it's very high still, even though we've been getting it to come down.

DR. SUYDAM: That's fine. Thank you, Dr. Walson.

DR. DURE: So there's not really any data.

DR. WALSON: Not that I'm aware of.

DR. SUYDAM: We have national survey data from parents.

DR. DURE: Right, which is not

DR. SUYDAM: Not what you're wanting.

DR. DURE: Not really what I'm asking. Okay.

DR. TINETTI: Dr. Cnaan.

DR. CNAAN: Yes, first, I want to thank all the speakers. My question is for the industry representatives as well. At the end of the day, what we saw is that the

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only efficacy data from trials is from the last decade or so is all negative. What I don't understand in all the plans is why are there no plans for good, large, simple randomized clinical trials adequately controlled, adequately designed and adequately analyzed at the end of the day?

DR. SUYDAM: I'd like to answer that question. We are committed to doing the pK studies. We are not sure that it's necessary to do the efficacy studies. We would like to get some consensus from FDA and pediatric experts on end points and on validated methodologies and we know there is some work going on right now, although it is proprietary, on both of those topics. And then we think we need to discuss with the FDA if and when or how we should do the efficacy studies if they're deemed to be necessary. We are not precluding efficacy studies. We're just saying at this point it's premature for us to commit to those without having those other things already aligned.

DR. TINETTI: Dr. Taylor.

DR. TAYLOR: To the petitioners, we talk about a number of ages and age cut offs 2 years during the

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various presentations 2 years, 5 years, 6 years and your petition is for 5 years and I'd like to have some further discussion of the evidence that suggests that that's the appropriate cut off in this case.

DR. SNODGRASS: I'm not sure the data will support

that as being appropriate cut off. I would think that the data that I'm aware of is that beyond that age, as I mentioned earlier in the morning, there is lack of efficacy as that data was done. So this gets into what was just asked earlier about further trials in efficacy. It's one thing to state efficacy. I think effect size in future studies will be important, so you can have the 6 percent figure cited for the adults is one figure, but you need to get the effect size on how that's designed.

But in terms of 5 years versus 6 years versus older or younger, the data that exists right now is that there is data that above that age range they're not affected.

DR. TAYLOR: So the age was selected because of the safety issue. That's what precipitated all of this, but you could have chosen a different age if you're looking at efficacy.

DR. SHARFSTEIN: I think we would agree with that.

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The age was chosen primarily because of the urgency we felt around the safety under 6.

DR. TINETTI: Dr. Cohen.

DR. COHEN: Thank you. This is for Dr. Abate and then also if I can get follow up from Dr. Suydam as well. But this relates to many of the issues that Dr. Abate raised with medication errors. He really presented quite a few error modes and I guess when you hear about them you wonder how it is that that could go on and on and not be addressed by FDA.

But I'm also aware, although probably a lot of people are not familiar with the fact that the regulatory authority isn't necessarily with the people that are talking about it today with the monograph drugs at least. And that, including advertising is really with the Federal Trade Commission, not the FDA. So I guess the first question I would ask is what do we need to do to do the same things we do for OTC drugs with or with prescription drugs rather for the OTC drugs?

And then, in follow up, I'd like to ask Dr. Suydam with the Consumer Healthcare Products Association she did mention, and I congratulate her for the educational

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efforts, et cetera, but we all know that's not enough to reverse some of these problems that Dr. Abate mentioned.

So I'd like to hear some follow up from her.

For example, the line extensions, the brand name extensions that were discussed, you know, that seems to be presenting a problem. I know from personal experience with our reporting program some of the labels don't even have of the immediate container don't necessarily have the active ingredients and they don't appear, necessarily, on the front label panels. Some manufacturers do that. Other just pretty much include the symptoms. So as far as recognizing the drug names, that's a problem. So if I could get both of those.

DR. TINETTI: Maybe you can clarify that question first. Is your question what authorities FDA have themselves in terms of clarifying the label information to avoid some of these medication errors? Is that your question?

DR. COHEN: It is. And many times we've presented information to the FDA and they tell us that they really don't have the authority, the regulatory authority at all to do anything about these.

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DR. TINETTI: Is there somebody from the FDA who wants to respond to that question?

DR. GANLEY: I just want to get clarification. Is your question what authority we have to mandate certain types of labeling on...

DR. COHEN: Well, to address the issues, for example, do you review the products prior to marketing? Do you look at the advertising, et cetera, because we saw some ads

DR. GANLEY: No.

DR. COHEN: -- you know, could be considered misleading by some.

DR. GANLEY: Right. The way the monograph is set up there's no requirement, pre-approval by FDA. The company simply has to get an NDC, new drug code, number and they market the product as long as they follow the monograph, follow good manufacturing practices and following the labeling standards in the drugs facts regulation. There is no requirement for them to send in anything for pre-approval.

With regard to advertising, we have no authority over the advertising of over-the-counter drug products.

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As you mentioned, that's with the FTC.

DR. TINETTI: I think his question was a little bit different, not do they have to come to you for approval. But these clear-cut cases where it is confusing can you regulate the drug labeling regardless of whether they're required to are you able to, not necessarily are you required to.

DR. GANLEY: Well, I think it depends on we do have the authority if we believe that the product is misbranded.

DR. COHEN: I mean even before that occurs, you know, screening the products. The prescription drugs they would be screened.

DR. GANLEY: We don't have a requirement that it needs pre-screening.

DR. COHEN: And really my question was how can that be addressed because it just doesn't make sense to a lot of people. I think that doesn't take place with over-the-counter drugs with the problems we're having.

DR. GANLEY: Right now, I don't think we have the authority to require someone marketing under the monograph to send something in and I don't know at minimum it would

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require a regulation. At a maximum, it may require another law. So I don't know what the legal ramifications are to mandate something like that.

DR. COHEN: It just seems to be a fundamental problem here.

DR. JENKINS: John Jenkins to follow up. When we write the monographs for the labeling, we talk about what needs to be there, but the monograph doesn't specify about the trade name, for example. So we specify about the established name, the indications those types of issues. A lot of what you saw in the presentation was trade name confusion, line extension of the same trade name used over and over again. We've raised this concern in the past. Everyone of my age and older probably thinks of benadryl as being diphenhydramine. But over time Benadryl as become just a trade name for a company's line of products, many of which contain diphenphydramine, many of which don't, for example. So our monograph talks about labeling required as far as the active ingredients, the statement

of identity, the indications, the dosing, warnings, et cetera, but not the trade name.

DR. SUYDAM: May I, Madame Chair? First of all, let me try to put it in context. I think we're talking about a very small number of adverse events with millions of products that are sold. We have most I'd say the vast majority of parents know how to use these products safely and effectively. And definitely we want to work to make any confusion less confusing. So we can do that.

We think we can work to bring awareness to active ingredients. We know that it is one of the things that consumers are least familiar with, but they are familiar with symptoms and if you look at the label, the active ingredient also then has the symptom in parentheses next to it on the drugs facts label. So it helps parents match products and we understand that this is what parents do.

David, do you have a slide?

(Slide)

DR. SUYDAM: In our survey of parents, we asked them how familiar are you with active ingredients. Slide on, please.

(Slide)

DR. SUYDAM: And you can see that parents say they are somewhat familiar, quite familiar; but about 15 percent say they are not at all familiar with the active ingredients. So we think we have an educational opportunity to encourage parents to understand what the importance of the active ingredient.

(Slide)

DR. SUYDAM: The next thing about selection we also know that parents trust brands. That is something they look for when they go to it and they understand the dosing mechanism for the brand that they're choosing. So if you would go back, this slide on, please.

(Slide)

DR. SUYDAM: This shows you how familiar are you with the part of the label that says the symptoms that it treats. And you'll see that the very familiar and quite familiar are at the high numbers on this one. So parents know in their minds they go for what symptom are they trying to treat and they look for that on the package.

Thank you.
DR. TINETTI: Thank you. Dr. Daum.
DR. DAUM: So this is a question for industry again. I'm sorry. You keep trying to sit down and I apologize for bringing you back up.
DR. SUYDAM: I'll be glad to stand here.

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DR. DAUM: Well, good. So I keep thinking of these pictures that we've seen of showcases within pharmacies of the products intended to treat common colds and I'm a pediatrician and I would like to see the results of pediatricians or practitioners dealing with the same survey you just showed. For parents data I think you'd find, particularly if you ask questions about their factual knowledge, parents wanting and pediatricians wanting.
But my real question is this what do think that industry has created here in terms of being helpful to parents and consumers and children, for that matter. It looked to me like a bewildering in fact, when I go to the drugstore, it looks to me like a bewildering mess of complicated ingredients, combinations that do and don't make sense, lack of information about what the products are supposed to convey or deal with.
This business of consulting with your doctor if your kid's under 2 and people call me, I don't know the answer. So it looks like a Tower of Babel rather than a constructive marketplace. And one of the constructive ideas I kept hearing this morning was that there should be

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single-ingredient products on the market. And perhaps with education and some efficacy and safety data, they would make more sense.
Why do you think that you all have created a system like this? And then, secondly, what is your response to the idea that single-ingredient medications with all the hype and the check marks and the pictures of babies who would possibly be better?
DR. SUYDAM: Well, first of all, I think you've put a lot of things into that question.
DR. DAUM: I apologize for that.
DR. SUYDAM: We do agree with you that there is confusing about "consult your doctor," which is why

suggested in our recommendation to the FDA in September that we would change that to "do not use." And it's also why we voluntarily withdrew all of the products from the market that said "infant" or had pictures of infants on the products.

But what we've created for consumers are two things, actually three things. Brands that they trust, choice because parents want choice and access, and not all children have the same symptoms at the same time. And

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they treat only the symptoms that their child has.

And the other thing about combination products that people haven't mentioned is I think it's hard to get children to take medicines. And if you know that your child has a cough and you know that they have a runny nose and you're able to buy one product that treats both of them rather than trying to give them two products at the same time, I think it's a very effective way for a parent to manage their child's illness.

And I think that's what we see and that's what consumers want and we hope and believe that we absolutely can help parents to learn how to use products appropriately. That's what we want. Safety and safekeeping of our products is our number one priority. That's what we want and our education program will be designed to try and deal with people so they can help treat their children more effectively.

DR. TINETTI: If I could just have a follow-up question to that. It sounds like a very nice program. It sounds like a lot of bells and whistles. But the question is that the proof is in the pudding and the details and everything. Give us an example of a previous educational

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program that we can say, okay, now this has happened before and this effect.

What precedence do you have for this kind of a multifaceted educational program and how can you convince us that, number one, you're going to do it; umber two, you're going to reach the people; and number three, there's going to be any measurable outcomes that makes it worthwhile?

DR. SUYDAM: Well, number one, we are committed to doing it and we've said it publicly and we'll be

DR. TINETTI: Start with the precedence of other studies, a similar example.

DR. SUYDAM: Okay. There are some other there are other education programs that have worked and we are committed to doing

DR. TINETTI: Can you tell us what it is just so we can

DR. SUYDAM: Well, Reye'S Syndrome is one. There are other behavioral kinds of things that people have done for children that are fairly successful that we can use as models as well that have changed behavior significantly. And we think first of all, you have to raise awareness.

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You have to then change attitude and behavior and then you constantly measure to find out how much you have changed the attitude and behavior. And you have to reach out to new moms. So you start with the baseline and get to those people before they start treating their children.

DR. TINETTI: So the Rise Syndrome is the only example I mean that's a wonderful example, but it was a very clear-cut example. Don't do it.

DR. SUYDAM: Yes.

DR. TINETTI: What you're talking here is a much more nuanced thing. Do you have another sort of nuanced example?

DR. SUYDAM: No, I do not. And I think it is a complex program and I think it is something that we are dedicated to working on. And as I said, it's a very small number of parents who are not able to use the products at this point in time and we want to make them more effective.

DR. TINETTI: Dr. D'Augustino.

DR. D'AUGUSTINO: My question actually revolves around some of this discussion that you just had. I was getting very excited when the presentation was made from

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the industry that you know, we were talking about you needed clinical trials with pediatric end points and then it shifted to pK studies. And the more I heard about the pK studies the more frightened I got that you would be talking, if you had a new drug that you were looking at and nobody was taking it on the market except for in the clinical trials, you could be doing a lot of these

bridging studies and pK studies while you're running them.
But I mean it sounds like it would be years before you resolved the pK issue. What happens in the meantime? I don't see this as a quick turn and I think the clinical trials would probably be clinical trials with these pediatric end points, and maybe you don't have any, would somehow rather be more apt to reach fruition. So I'm confused in terms of why you think you can pull off the pK studies where it looks like we really have any evidence of what's going on in that population.
DR. WALSON: Yes, first, as a member of the PPRU, Pediatric Pharmacology Research Unit Network, funded by NIHD, that specifically targets pK studies we have 13 centers. There have been a total of about 20 that have been funded over the years since about 1990. PK studies

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are not slow. You can do a well designed, population pK study in a year, six months.
DR. D'AUGUSTINO: If you knew what to look for. I'm confusing we don't know what goes on with these 2 to 6-year-old children and now we're saying we can extrapolate, we can bridge and so forth. I mean we don't have any studies there. We have no confirmation of what's going on. I mean if you were moving a drug into Japan and they don't have a way of running a big study, the pKs work fine. I'm not so sure that they work here.
DR. GELOTTE: I hear your concern. I think one of the key points about the pK study is when we differentiate between the ages 2 and 2 to 12, and we're talking about 2 to 12. Most of the maturation in renal function and empathic function has occurred.
Dr. Roy went very carefully through a lot of the maturation with metabolism and that is mainly occurring from zero to 2. When you get to 2, there can still be changes, but we wouldn't be shooting in the dark. We'd be doing the studies with pediatric experts who have experience in these pediatric pharmacokinetic studies and you really need to do that as the first step.

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We need to confirm or adjust the doses and then again, thinking about the clinical research plan with the agency, then we would want to take a look at are there any types of

DR. D'AUGUSTINO: That's where I'm going. You run the pK studies. You have something. Then you need to verify that it works and efficacy and that seems not to be what you're saying if I hear you correctly. I mean that's exactly the program I thought you were going to say and you were going to have pediatric end points and so forth. But it didn't seem to materialize.

DR. TINETTI: I think that already was spoken to and they said that basically the FDA told them they needed efficacy studies they'd be willing to do them. So I think, to some extent at least, that's been addressed.

DR. SHARFSTEIN: But you don't feel like efficacy studies are needed. That is what Dr. Suydam said a few minutes ago.

DR. D'AUGUSTINO: Yes, I don't think you need to dismiss it so fast.

DR. SUYDAM: I said we didn't rule them out, but we really want to

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DR. TINETTI: Let's take it in order.

DR. D'AUGUSTINO: But I also heard them saying they don't think they need to be done and that was not in their plan. I mean their arms can be twisted and so forth, but that drags out another set of years. I'm not so sure we have a rapid response to the issue we're talking about.

DR. TINETTI: Well, we'll have certainly more discussion on that tomorrow. That's one of the things we're charged with. Dr. Celento.

MS. CELENTO: Actually, I'm not a doctor. I'm a patient representative, Amy Celento. I have two questions, one for industry and one for the petitioner. The question for industry is around what you will do in terms of the educational campaign.

I realize what you're presenting here very top blind, but I have concerns about the fact that you have not mentioned anything about multilingual campaigns or addressing cultural issues and you haven't talked about the use of images.

I have some concerns. Recommendations to just say, "do not use" or "do not use to sedate children" is very general. It's not a visual image. People don't get it,

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especially if they're panicked and they don't know what to

do for their kids.

DR. SUYDAM: Those are very helpful suggestions and in fact, things we have talked about. We obviously have conducted multi-lingual campaigns in the past with some of other educational efforts and this will be part of that as well.

And obviously, we need to think about the wording "do not use" or "do not sedate" as what is that? Is that appropriate? And if the Committee feels we need to do a label comprehension on "do not sedate" so we could find out what does that really mean to the consumer we would be happy to do to that.

I think "do not use" is a simple phrase. When we tested with one-on-one interviews that we did with caregivers, it was very clear to them what that meant and their reaction to it was very clear, which was that they would not use the product. So yes, we're open to all of those suggestions.

MS. CELENTO: And my question to the petitioners sort of ties into this. Telling parents do not use for children under 2, many parents have multiple children.

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They may be using the product for children 2 to 6 to 12. When they're told by you, no, don't use it, what are you going to recommend the parents do because some parents will say it works for my 6-year-old. I'm just going to use it for my 2-year-old.

DR. SHARFSTEIN: That's a good question. When we started this back in October 2006, we made sure, as a public health agency, to be giving affirmative recommendations, not just saying don't use this, but actually what you can do. And we put a page up on our website that explains a number of things, how important it is to keep kids hydrated, what symptoms to look out for and a few other kind of common sense things.

And I think it is important I think one of the key things that we're asking for in the petition is for the Food and Drug Administration to explain that the products have not been shown to be safe and effective and that they should not be used.

And as part of that communication, it will be important in multiple languages, to multiple communities not only to send that message but to provide guidance on

the kinds of things that help kids when they're sick.

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DR. TINETTI: Thank you. Dr. Newman.

DR. NEWMAN: I have a question for Dr. Kuffner. Dr. Lopez reviewed results of 11 clinical trials, but in your slide you said you reviewed 54 published and unpublished clinical trials, so that leave 43 clinical trials that apparently have never seen the light of day.

And in past committee meetings sometimes those have been industry-sponsored trials that fail to show efficacy and I'm just wondering can you tell us more about these 43 or however many there were unpublished studies. What they found for efficacy and whether they are ever going to see the light of day?

DR. KUFFNER: For the safety data that we reviewed, they weren't just efficacy trials for a cough and cold indication. This was any time that a child under 12 years of age or under 18 -- we categorize them differently were actually exposed to the cough and cold ingredient. And so I think that may explain the difference between studies that were definitely done for efficacy of a cough and cold indication and studies where children were exposed to these medicines.

DR. NEWMAN: But did any of those trials have

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efficacy end points?

DR. KUFFNER: Many of the trials did have efficacy end points.

DR. NEWMAN: What did they show?

DR. KUFFNER: We could go through we have slides for each of the ingredients from a safety perspective. I don't have the slides for each of the individual studies from an efficacy perspective.

DR. NEWMAN: Were there any that showed efficacy?

DR. KUFFNER: That I'm not sure of. I reviewed them from a safety perspective, from an exposure perspective.

DR. NEWMAN: And could we get access to the efficacy results somehow?

DR. KUFFNER: Sure.

DR. TINETTI: Thank you. Dr. Parker.

DR. PARKER: This is a follow up to Dr. Abate's comments and a question to the FDA regarding that and also to industry.

I think you captured well in your presentation that variability is a source of confusion. If stoplights look 20 different ways, most people probably wouldn't stop and we'd have a lot more wrecks. And if dosing is presented

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in multiple ways and dosing devices look differently, it no doubt is a source of confusion and misunderstanding and probably medical error.

So the question last week there was a presentation at the IOM Roundtable on health literacy that looked at medical labels, an event that's at the intersection of health literacy and patient safety. And there was a presentation by Allister Wood to look at the possibility of the uniform medication schedule for dosing medications.

So my question to you, you posed to us to consider this idea of requiring well-designed and product-specific dosage devices. My concern would be if we end up with 10 new and improved different ones and whether or not on the end of that we're going to have improved ability to safely and effectively take any medication. So not just new, well designed and improved but perhaps standardized.

And then opportunity for major manufacturers to come to the table and say we're about the same thing and whether or not there is some way to look for a win in this for everyone that this may represent an unbelievable opportunity to try to do something right that in the end could help the ultimate person that we want to help and

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that's our patients. So I'd like to hear you both respond to that.

DR. ABATE: Ruth, I'm not sure what the question is.

DR. PARKER: The question would be sort of a willingness to look at a standardization of dosing and dosing devices

DR. ABATE: Dosing instructions?

DR. PARKER: Yes, dosing instructions, dosing devices. We have a standard drug format for the over-the-counter product with regulatory oversight of the drug facts being on over-the-counter products. But the specific language that governs how doses are presented and the devices used for being able to take those, and whether or not looking at a standardization of how those are done so that, like I said, we don't end up with not new and

improved for one; but new and improved that crosses and the ultimate person, the patient, has one way that they need to learn how to safely and effectively use whatever product it is.

DR. TINETTI: Ruth, are you talking about regardless of the products of all those 300 we saw, you're talking about regardless of which product they pick off the shelve

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the dosing instructions will be exactly the same. Is that what you're saying?

DR. PARKER: Yes, to decrease variability.

DR. ABATE: The way the monograph is set up is they should be pretty much the same. It should be the same language because it's codified in a regulation. Now, the issue I think we're going to address cup issues and I think the Office of Compliance who sort of oversees the issues regarding devices such as the cup in there can also comment on the standardization of dosing instruments. But the language and instructions are codified and so there should not be much deviation from that from product to product.

Now, where there may be differences, though, is that there's variability allowed in the concentrations. So you know, you're probably aware that there are different tablet strengths and different concentrations and the monograph pretty much allows leeway within a certain concentration to permit marketing. In fact, I don't think for most of them they don't even require a specific concentration or a specific tablet size, but the instructions have to be consistent with regard to is it

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every four to six hours or whatever.

But the way the monograph is written is it inserts tablet size or teaspoon. Okay. So if they're supposed to take two teaspoons for one concentration and one teaspoon for another concentration, that's where you're going to see variability. But I guess are you getting at that they should be all standardized concentrations also.

DR. PARKER: I think the closer at least what we heard in that presentation was really that the closer we get to finding one way to say the same thing the greater the changes to improve comprehension on the other and decrease medical mistakes. So for example, we know that

"take one pill once a day" this was presented last week was written 44 different ways by prescribers when really you could say it one way. And it's subtle difference and yet for patients who are trying to line it up and take it that is a source of confusion, and so the idea just being to figure out how close you could get in a standard with federal oversight because it's over-the-counter and it's on drug facts.

DR. GANLEY: I think we are closer to that with these drug products than the prescription products you

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talked about last week at the ION meeting because there is a required standard language in terms of if it needs to be every four to six hours or every six hours or whatever, which is the problem on the prescription side where three times a day could be Q eight hours. It could be TID is multiple variations and that includes the prescribers, but also there's variation in how the pharmacists dispense it.

But I think we're actually closer to that with these products than we are with the prescription products.

DR. TINETTI: That sounds like that's a great thing. Sounds like something probably for more discussion tomorrow. I think we're going to take our break now and everybody is back by 10 minutes to. Thank you.

(Recess)

DR. TINETTI: I think we're going to reconvene if everybody would take their place and hopefully, have gotten reinvigorated for our continued questions. And I guess we'd like to certainly some discussion is fine, but remember the point of tomorrow's meeting is the discussion. So we'd like to focus as much as we can while we have all the people here to focus on questions and limit the amount of discussion for today because that's

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our focus for tomorrow.

Next on our list was Dr. Gorman.

DR. GORMAN: I'd like to ask some questions about CHPA.

DR. SUYDAM: Yes.

DR. GORMAN: As a member of the Academy of Pediatrics, we are mainly a United States organization with some global reach, would that adequately describe the CHPA?

DR. SUYDAM: Yes, that's correct. We are United States based.

DR. GORMAN: We are mainly a policy organization, not a regulatory organization. We can state what we would like our members to do, but we can't force them to do them. Is that a good parallel with your organization?

DR. SUYDAM: I can't force my members to do anything, but they have all committed, every one of them who are a part of this group, to do the things that we have laid out in our plan today.

DR. GORMAN: The world of pediatric healthcare providers is fairly large and the number of pediatricians is fairly small. Are all the manufacturers and marketers

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of these agents in your organization?

DR. SUYDAM: We have about 95 percent of all of the sales of OTC products within the organization.

DR. GORMAN: So Wal-Mart is a member of your organization?

DR. SUYDAM: No, Wal-Mart is a retailer. They are not a manufacturer or a distributor.

DR. GORMAN: Would they have some say over the packaging that they provide for their products?

DR. SUYDAM: No, they do not. Those reside with the manufacturers.

DR. GORMAN: Does CHPA have a scientific arm that does studies?

DR. SUYDAM: No, we work with outside scientific organizations.

DR. GORMAN: Do you have a budget in mind for these pK studies you have proposed?

DR. SUYDAM: The pK studies are being done by individual companies. Each one has been agreed to by an individual company, some of which are already underway and in discussion with the FDA.

DR. GORMAN: Would you be willing to provide this

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committee a list of the companies that have agreed to do these studies on what are basically commodity products?

DR. SUYDAM: Yes.

DR. GORMAN: Thank you.

DR. SUYDAM: If I could come back, Madame Chair, with one response to perhaps I left an impression that we

were dragging our feet on the efficacy issue. And if I have, I apologize because that is not at all our intent. When I say we are committed to pK studies, that means we are doing pK studies and we are working with the FDA as quickly as possible to get these done. And we know we have to work within the pediatric community as well. And we are committed to doing what needs to be done, including efficacy studies. And I think if I left the impression otherwise, I want to make sure that that's changed and that you know we will do this as quickly as possible.

DR. TINETTI: Thank you. Dr. Joad.

DR. JOAD: Just as a quick follow up to that one, so you've said that the organization is going to do a large, properly done efficacy study. Is that what you just said?

DR. SUYDAM: I said we're committed to doing the efficacy studies and we will work with the FDA on how they

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should be done.

DR. JOAD: Okay. My question, and I don't know if this go to industry or FDA was the antihistamines appear to be first all first generation. Is there a reason there are no second-generation antihistamines in the cough and cold preparations that are over-the-counter?

DR. JENKINS: Those newer antihistamines would be in NDAs. They're not in the monograph. So for example, the Loradin products that are on the market are either on NDA or a generic, which we call an ANDA, so those have to be product-specific applications versus the monograph process that applies to all the older drugs. It's not surprising that the monograph has all the older antihistamines.

The newer antihistamines like Loradin are NDA products go through a switch process to go from prescription to nonprescription. And as one of the presenters earlier noted, those are product-specific reviews versus ingredient-specific reviews.

DR. TINETTI: Dr. Dure.

DR. DURE: That was a while back, but I do have another question. This is for the FDA. I believe that one of the speeches or talks this afternoon had to do with

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an educational program and I guess this was in the efficacy talk. What would the content of the educational program be? I mean would it be that these drugs there is

not insufficient evidence to endorse efficacy of these agents?

DR. JENKINS: Well, you know, I think that's what we're asking the Committee to opine on. So the contents of what the program would be about would be, in large part, related to what you recommend about the safety and effectiveness of these products, the ability to extrapolate, which I haven't heard much discussion around the Committee table yet about whether you agree in philosophy with the concept of extrapolation. So I don't think we can say what the content would be until we know about what the Committee's recommendations are and what actions we would choose to take as far as altering the monograph.

DR. TINETTI: I'll take the bait on that one. One of the questions that hasn't been addressed yet; and in none of the talks actually have we had much of a discussion. So perhaps this would be the petitioners might begin and maybe the FDA could follow up is our

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understanding is extrapolation is appropriate if there is compelling evidence that the biologic activity of the disease and the response to the drug should be the same regardless of age, and therefore extrapolating from an adult to children is appropriate.

And I guess maybe perhaps begin with the petitioners, any actual evidence in data rather than an opinion to support whether or not there is evidence to support that extrapolation is appropriate, using those criteria.

DR. SNODGRASS: I'm not aware of data that answers that question. There are reasons to think physiologically it's been mentioned very briefly smaller airway size, smaller nasal passage size, but in addition the issue of nasal congestion, rhinorreha, which the later is more of a coallergic phenomena. The developmental age-related response and action of those processes is not well studied and there may be some differences, but I'm not aware of data.

DR. SUYDAM: I think we have a slide that would show you some data that might be useful if we may. Slide on and Dr. Walson will speak to it.

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(Slide)

DR. WALSON: Well, first, I should say that Wayne couldn't be aware of this. It's in press, so there's no way that Dr. Snodgrass could know about these data. But these are data in press on one of the key issues of extrapolation, which is, is the course of the disease the same in children and in adults?

And it's a little complicated. So yellow is nasal congestion, top children lower yellow line adults; blue runny nose, children and adults; cough, again, children and adults and children, however you want to do it. I think the key issues here is the time course. While there's quantitative differences in the number of children versus adults that report or have someone else report a certain symptom, the time course is very similar.

It's also very important because we made this point as well as Dr. Lopez made this point. Studies done in those first three days when symptoms are getting worse are very likely to have a different effect size than studies done at five to seven days when everyone's getting better.

DR. SUYDAM: Thank you, Dr. Walson.

DR. TINETTI: I'm not sure that addresses the

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question of the physiology and anatomy of the disease. So what I'm hearing is at present there really are no none data to say that children and adults have the same other than obviously there is some anatomic difference the question is, is that a studible question? Could we get a is there a way to study that question to look to see if the physiology and anatomy really does affect the manifestations and response to treatments differently?

DR. SNODGRASS: Well, I can only give you an opinion. I think that if enough effort were directed in that direction, yes, there's techniques that probably could be applied to getting airway resistance in younger infants, for example, that would be relatively lesser or even non-evasive essentially. Are they available? I don't specifically.

The data that was just presented I think the question gets back to extrapolation and I appreciate what that data is and the difficulty of even getting that data, but can you exactly extrapolate from that data? And so you need objective measurements if that's possible.

DR. TINETTI: Let me ask the FDA the question on extrapolation. Is your standard that there needs to be

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evidence to support the appropriateness of extrapolation? Or is your standard that if there is not evidence to support extrapolation then the assumption should be that it's not appropriate? I don't know if I made that question clear.

DR. JENKINS: Well, I think you can refer to DR. Starke's presentation. Slide 4 gave you the actual language from the statute, remembering that PREA codified the ability to extrapolate. And it says, "The course of the disease and the effects of the drug are sufficiently similar in pediatric and adult populations."

That's the standard for deciding whether extrapolation is acceptable. And his slide went on to say that that can be supplemented by information about dosing, pharmacokinetics, and safety in the appropriate pediatric age groups.

His next slide then talked about some of the factors we consider as we make decisions about extrapolation. He described we've long extrapolated efficacy in allergic rhinitis and he described some of the characteristics about allergic rhinitis that we have no reason to believe are different between adults and kids. And I think

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there's actually data suggesting that they are the same.

For example, mass cell degradulation and the impact of histamine on the permeability of membranes, et cetera. So I think the real question before the Committee is whether you believe that the common cold and cough can be reasonably extrapolated between adults and children. And you made a comment earlier that there's no data to demonstrate that. I just heard that from Dr. Snodgrass and he wasn't aware of any data.

I don't know if Dr. Starke or anyone else from the pulmonary division wants to comment, but I don't know that I would accept that that's the actual state of the science. We know it's the same viruses, for example, and the response of the mucus secretion, et cetera, may be very similar. So I think the position is that we look for evidence that the disease and the likelihood that the response is similar. It may not always be 100 percent

confirmatory from clinical studies.
You have to make a judgment and we're asking the Committee today and tomorrow to make a judgment in colds and cough do you believe it's reasonable to extrapolate data from adults to children and if so, what age groups,

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what ingredients, et cetera. You may conclude that it's reasonable and still conclude that the benefit/risk equation in certain age groups is unacceptable.
DR. TINETTI: I think we'll move on unless Dr. Starke had anything else to add.
DR. STARKE: The only thing I can add is that, first of all; you have many different cold viruses. So you're not dealing with one straightforward disease and you have mediators, a multiplicity of mediators, so it's not as simple and straightforward as allergic rhinitis, which the mechanisms of which I learned in medical school many years ago. So you have to decide whether all the sidacambulis (phonetic) and so on are all whether the medications match up appropriately to the disease, the multiplicity of events that are going on in the disease process.
DR. TINETTI: Did you have anything else on that particular point of extrapolation?
DR. SNODGRASS: Yes, it's dose response is what you want and depending on the mechanism of the drug, there are age-related differences known for narcotic receptors. There are age-related differences that are known for immune responses. So I think it would predictable that

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there would be age-related differences in dose response and efficacy affect size.
DR. TINETTI: Dr. Neil.
DR. NEIL: Question for Dr. Suydam following up on Dr. Gorman's question. Within your organization last week you announced a voluntary withdrawal of 14 branded products, and aware that at least one member company of your organization manufactures products for store branding.
Could you expand on
DR. SUYDAM: Those were removed as well.
DR. NEIL: Thank you. And so the other part of my question ahs to do with the voluntary nature of the withdrawal. Given that it sounds like all of your member

companies have voluntarily withdrawn these entities for children under 2, would you support that that withdrawal be made mandatory or if not, have you considered how long this voluntary withdrawal might exist. Is this a permanent phenomenon or until such time further evidence comes to light?

DR. SUYDAM: As far as we're concerned it's a permanent phenomena until there's other evidence that

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would change our thinking on this. And I think at this point we don't see any evidence in that, even heading in that direction.

DR. TINETTI: Dr. Rappley.

DR. RAPPLEY: My question is for Dr. Roy. I thought you did a really fine job in presenting the very many ways that children are different and are different over time and how they metabolize medication. And I am thinking about the genetic variability and polymorphism. So I want to tell you how I think about it and I want to know if this is a reasonable way to think about.

So of the six products we're looking at, five of them are metabolized through hepatic sacrum systems. One of them is well known to have at least hundredfold variability in 5 to 10 percent of the Caucasian population and 1 to 3 percent of the Asian population. I presume that it's not studied in African Americans and other ethnic groups or you would probably have that information for us. So at least five of these products could have similar variability.

When we are talking about children and very small doses in terms of the range of dosing, so whether it's 15

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to 30 milligrams or 1.25 to 2.5 milligrams of a medication, we're thinking about a very small range that's safe to give a child. These children are subject to the same genetic variability. And so are they at greater risk for an unanticipated consequence being a super metabolizer or a slow metabolizer because the dose range is so small?

DR. ROY: That's a good question. I don't think we have studied enough in children to answer that question. We can make some speculations.

DR. RAPPLEY: I'm asking you to speculate. I mean, as we think about the whole risk/benefit ratio, if,

indeed, 10 percent of the population could have a hundredfold difference in who they metabolize these medications we're discussing, then parents need to understand that when they make decisions. Physicians need to understand that as we do with other types of medications tricyclic antidepressants and other things. We know that about those prescription medications. We do drug levels. We take certain steps. We're not yet able to study the polymorphism and predict for an individual, perhaps not commonly. So I'm wondering if you believe we should factor this into our consideration of the risk for

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young children.

DR. ROY: The short answer is yes, absolutely. Just the fact that the hundredfold difference, you know, so the risk tolerability could be very different for children versus adults. We know these things create problems even in adults. So that's the state of the knowledge right now and I think this is, again, a lot of the other things that the agency is doing is also one of the things is individualized medicine and all that. So that's a whole different set of discussion, but it's related to some of these issues.

DR. SUYDAM: We have some information on that. I think Dr. Gelotte will speak to it.

DR. GELOTTE: Well, what we're aware of it's not data for children, but there has been a prospectively designed study in adults giving up to 10 times 330 milligrams of dextromethorphan every six hours. So that's 10 times the amount. It's an older study in 1991, so they weren't clear on whether they were fast metabolizers or poor metabolizers.

But from this controlled prospectively designed safety study, at those high doses, in adults at least they

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didn't see any major effects. They were minor that were rapidly reversible dizziness and slurred speech, but it was the only data that we're aware of the higher doses. So again, perhaps they're all fast metabolizers or extensive metabolizers, but it's a little bit more data that may be helpful.

DR. SUYDAM: And I think in Dr. Dart's chart he pointed out the therapeutic ranges that they use as

referrals to the poison control centers using as referrals to hospitals.

Dr. Dart, would you like to speak to that, please, because I think that has something that would be helpful to this.

DR. DART: Could you show that slide, please?

(Slide)

DR. DART: Dextromethorphan is one of the ones that we had actually national consensus guidelines from all three clinical medical toxicology organizations. That's the poison center organization, the American College of Medical Toxicology and the American Academy of Clinical Toxicology and you can see for dextromethorphan the ratio.

So depending on which part of the FDA you chose, at

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the least it's a tenfold referral dose for dextromethorphan.

DR. TINETTI: How are those decisions made, on what basis were those levels

DR. DART: That was a HRSA funded project, Health Research Service Administration. Basically, all three organizations put forth members to meet. They discussed it in a there was a dedicated group that generated information. So medical literature was pulled. The American Association of Poison Control Center dataset was analyzed and then it was a consensus process after that, pretty much a typical one where the came up with that.

DR. TINETTI: Dr. Rosenthal.

DR. ROSENTHAL: Well, actually, my question was just asked by Dr. Rappley in a much more eloquent way than I had planned to do it, but let me beat the dead horse then. I'm still trying to get my arms around the safety issue and wondering whether there's an agreement all around the table regarding the susceptibility of certain hosts to toxicity from this group of drugs that we're talking about and the next part of that question, if there is agreement

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that there is a subset of the population of kids who are particular susceptible for whatever reason, I'm wondering if people can offer a guess at how prevalent that increased susceptibility might be.

DR. SUYDAM: I think, Dr. Kuffner, if you could,

please, come to answer this question.
DR. KUFFNER: Do you mind repeating the question, please?
DR. ROSENTHAL: I'm just trying to understand whether and if so, to what extent, there is a subset of the pediatric population that are particularly susceptible to toxic effects from this class of medicines that we're discussing either because of impaired metabolic pathways or altered metabolic pathways or because of other things going on like, you know, just to throw out an example, maybe a channelopathy that would increase their risk for an arrhythmia. And if you were to put all of those factors together, if you agree that there are factors, which increase susceptibility of a portion of the pediatric population to toxicity from these drugs, then how prevalent do you think it is?
DR. KUFFNER: So speaking from the data that we

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analyzed, and again, it was data over 27 years that we had within our database. Overall, serious events were very rare. I think one of the limitations of post-marketing databases is it's difficult to answer this specific question using this specific data.
DR. ROSENTHAL: Actually, that's not the specific question. I'm not really asking for the observation or the reported number of events because I think the events are likely to be under reported, particularly, for over-the-counter medications. And so my question is more on a physiologic basis. Do you think there's a group of kids who and the question doesn't have to be just directed to you. It can be directed to the petitioners as well. I'd like to hear other people's opinions as well.
But is there a group of kids who are particularly susceptible to the toxic effects of these medications, and if so, how prevalent is that? That's the question.
DR. KUFFNER: I think we know, in general, with any drug there may be people who are more or less susceptible, both from an efficacy perspective and from a safety perspective based upon the many years of use of these medications. If there is a susceptible population, it's

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an extremely low number or occurs very rarely.
DR. SNODGRASS: The only data I can think of at the

moment relevant to that is there's developmental animal data and a little bit of clinical data regarding beta receptors and angiotensin receptors in the heart and that a developmental process in terms of numbers of receptors, and also in terms of receptor response. So you could extend this to nasal congestion. What are the transporters for fluid, for edema or what are those factors or the receptors? Is there a developmental response difference? And if there were, then you would not be able to extrapolate. I don't know if that really addresses your question.

In general, if you look at where we've had the enzymatic, I'll call it, kinetic related, that is, the P-450 kind of data, you're talking about in the 3 percent, 5 percent, maybe occasionally 10 percent max where that's going to lead to enough of a change in the handling of drug that you're worrying about how that's being handled. So maybe to that degree that gives you a sense of that.

DR. TINETTI: Does that satisfied or your take home message we don't know. Okay. Dr. Clyburn.

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DR. CLYBURN: Yes, I think we asked the petitioners several times why they chose the 6-year-old number. I wanted to ask industry, again, why you chose a 2-year-old number, particularly, given that greater than 50 percent of chlorphemiramine and diphenhydramine errs serious adverse events and that convulsions are more common in the 2- to 5-year-old age why you chose 2 instead of 6?

DR. SUYDAM: There were a number of reasons. One is we thought 2 was a strong cut off in terms of physiological development. I think you've heard people say it's age 1, but as a matter of safety, we decided 2, assessing the most effective dose for someone less than 2 is more challenging. There were a higher proportion of fatal events in those children under 2.

I think if you remember Dr. Dart's charts, from all of the fatalities, you will see that 74 percent of them, I believe, if I've got the number correctly, were under the age of 2. So we think that they were the most vulnerable population to misuse. There is no labeling on the packaging for children under 2 and all of those reasons and then from 2- to 6-years old you've got a different issue.

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I think what we saw with the diphenhydramine issues is the sedation issues and Dr. Dart mentioned that in his presentation as well. I think there is this misconception with the number of people caregivers that you can sue diphenhydramine to sedate your child and it is not intended for that use and we want to make sure that it is not used that way and that's why we're suggesting a strong label on the antihistamines that say "do not use to sedate children" and we're promoting a safekeeping educational program because the other issue with 2 to 6 was the accidental ingestion.

DR. TINETTI: Dr. Ganley, you had a question you wanted to ask?

DR. GANLEY: Yes, I had a question for the petitioner and for industry, the petitioner first. You'd asked that it be limited to common cold, but the monograph allows nasal reduces nasal congestion, also for hay fever and it would see that if your argument is that there are anatomical differences between children and adults that make a differences in the effectiveness of those drugs why wouldn't it apply to allergic rhinitis as well as to the common cold? So I'm interested in understanding why you

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made that distinction.

DR. SNODGRASS: From my perspective, I don't know that there is a distinction. I think that potentially could apply to that age group as well for hay fever as a condition. I don't see why there couldn't be.

DR. GANLEY: So are you going to amend your petition then?

DR. SHARFSTEIN: I think that we saw the cough and cold products marketed for cough and cold, and the evidence around that as discrete from an allergic rhinitis kind of approach. And I think one of the reasons was that there is pediatric data for some of the prescription drugs, and antihistamines around allergic rhinitis and so that you know, and I think the way we looked at it partly, perhaps, preferred by the FDA scientists.

You talked about the pathophysiology of allergic rhinitis and I think the thinking is antihistamines and allergy is an area that has a kind of different history than treating infectious disease with these products.

DR. SNODGRASS: I think he was referring to antihistamines where it's hitting the source of the problem where it causes the congestion at the histamine

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receptor.

DR. GANLEY: Right.

DR. SNODGRASS: And this is a little different because we're treating congestion and does it make a difference whether the congestion is from a common cold or because of an allergy. It's congestion and so if your argument is that they're different based on anatomic, well, it should apply to both.

And I'll just also clarify that all the prescription products that have all the prescription antihistamines that have decongestants with them were approved without they were approved because there was already a finding by FDA in the monograph that a decongestant was effective. So they did not have to provide efficacy studies to support that.

So if we would go down and make this argument that decongestants aren't effective in kids from a regulatory point of view, it would be very difficult for us to make a distinction between a common cold and allergic rhinitis.

DR. SHARFSTEIN: You're not talking about the antihistamines for this question exactly.

DR. GANLEY: I'm just directing it at a decongestant

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understanding what potentially you know, if there's an outcome where the decongestants were not be getting a claim for the common cold, you know, we would have to adjust or change the monograph. It would also impact on, in my view, on the allergic rhinitis claim because you didn't address that in your petition and I guess I'm using some stupid logic here that if you have congestion it doesn't really matter what the source is if the ingredient is treating congestion.

DR. SHARFSTEIN: Okay, I didn't understand your question. I thought you were getting into the antihistamine issue. I'm going to defer to Dr. Snodgrass. That specific question we did not discuss when we put together the petition, but I see your point as well that you may have to deal with. But I don't think we can say more than that. I don't know.

DR. SNODGRASS: I can only really think in terms of mechanisms. I'm not sure I'm going to address your regulatory question very well. If an alpha 1 agnostic is constricting nasal vessels and you get decreased edema secondarily to that or if you've got a histamine mechanism decongestant or antihistamine, then it would make sense

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that the drug might have some efficacy.

But if you don't have that, then it doesn't rhinorreha I'll pick that one, for example. That's a coallergic mechanism. So unless you've got enough of an older generation antihistamine with some anticoallergic activity you're going to have no affect on rhinorreha. All right. That may not be helping answer your exact question.

DR. GANLEY: Okay. The other question I have

DR. TINETTI: I think that Dr. Rappley wanted to address that point as well before we go onto the other question.

DR. RAPPLEY: It just occurs to me that your question, and several other questions that have been voiced here, are begging a greater question. And that, is should we limit our discussion to using these medications in children 2 years and under or should we be considering yet a larger call for "do not use" due to lack of efficacy? And it was clarified very well by Dr. Taylor.

I'm hearing a lot of consensus and a lot of recommendation that, to the safety issues, we shouldn't use these medications in children under 2. But I do not

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hear that we're facing this question about the use in 2 to 12 around efficacy issues we're not dealing with that head on. Should we be dealing with that head on? This is perhaps the only opportunity to do so even if it's not in the petition?

DR. GANLEY: Well, it is in the petition, in essence, because it brings it to the 6-year-old age group. And so if you're going to say through all the pediatric age groups except for less than 2 because we've acknowledged we don't have data, it's been extrapolation. The panel that reviewed this came to the conclusion that the pathophysiology is the same. We expect the response to be the same and so we're comfortable extrapolating down

to 2 years of age, except for antihistamines they went down to 6 years of age.

DR. RAPPLEY: So are you saying it's either 2 or 12?

DR. GANLEY: No.

DR. RAPPLEY: Is that what I'm hearing?

DR. GANLEY: No, I think the issue is the petition has limited it to 6 years of age.

DR. RAPPLEY: Right.

DR. GANLEY: You know, one of the questions is going

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to address this is whether this also applies to 6 to 12.

DR. RAPPLEY: That's right.

DR. GANLEY: When we write regulations, we have to send it through a lawyer and the lawyers ask a lot of logical questions. So we have to provide a lot of logical answers to them. And so there has to be a lot of logic when we try to write a regulation that would say that these products are not available. I credit our lawyers for making us think in a logical and trying to be consistent manner.

DR. RAPPLEY: So I want to clarify then that the question before us is really a larger question than perhaps we asked as we started this day.

DR. GANLEY: Right.

DR. RAPPLEY: And that it applies to 12 and under.

DR. GANLEY: Well, as you see in the questions, we've allowed the Committee to decide are there certain age groups where they should not be available and other age groups where you're more comfortable but we may want something else to help bolster our confidence in what's out there.

DR. TINETTI: So to clarify then we could

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potentially say we think it's reasonable to extrapolate down to 6, but we don't think it's reasonable to extrapolate under 6. Is that something potentially that this Committee I'm not saying that they would, but I'm saying from what you're saying would that be something that we could do?

DR. GANLEY: You could do that.

DR. TINETTI: Something to support.

DR. GANLEY: Right. And I think you heard from Dr. Starke too that they recognized it's virtually impossible

to do a study in 2- to 5-years-old age range in terms of clinical efficacy. And so they based their extrapolation

DR. TINETTI: I'm not sure that's true. It's been done for Tavist. I think it's already been done.

DR. GANLEY: No, Tavist was done under 12 years of age.

DR. TINETTI: What age range was Tavist.

DR. STARKE: Twelve and above.

DR. TINETTI: Twelve and above, but nothing done under age 12.

DR. GANLEY: And they didn't seek a claim, from what I understand, for children and so they never received a

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claim. I think it's an important issue to discuss because whatever is recommended it has to be logical. We have to be able to explain it and it has to be supportable.

I just had another question and Dr. Sharfstein today pointed out or showed a lot of great examples of advertising, and as was noted, we don't control the advertising. But I think one of the things that wasn't addressed in the education program is what are you going to do about advertising? And I think the difficulty is that although the ads may be true, in that these products are probably generally safe, okay, but everything is relative here.

I think most of us will acknowledge that there are individuals that there have been adverse events to drugs. The ads really don't portray that and what I'm worried about is you may come out with an educational campaign that says something, but you're still spending $50 million on these advertisements that really have nothing in the ads that provides fair balance in that regard. So is there going to be some policy change in how you advertise?

The second question has to do with do we understand, number one, what "doctor recommended" means? This has

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been something that we've always had a problem with. We've asked for studies to document that. We've limited what we've allowed to be put on packages and this has always, I think, has been viewed by a First Amendment right by the industry on that. So we've asked, well, what impact does this have on the consumer when they read, number one, "doctor recommended" or number two,

"pharmacist recommended?"

DR. SUYDAM: Can I deal with your second question first? Actually, we have two surveys or studies that look at pediatrician's recommendation of cough and cold medicines. So could we put the slide on, please?

(Slide)

DR. SUYDAM: This slide shows the number of pediatricians who recommend -- and the number is in the thousands -- cough/cold products. Zero to 2 it's a little over 30, 2 to 6 it's just about 50 and 6 to 12, it's around 30. So those are numbers of physicians who are actually recommending. So there are physicians who are recommending.

We also have a study that we did recently or that was done recently with healthcare providers,

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pediatricians, family practitioners and nurse practitioners. Slide on.

(Slide)

DR. SUYDAM: And you'll see that, obviously, the lowest number of pediatricians recommending is in the less than 2 age as well as family practitioners and nurse practitioners. But the number increases and those are percentages, 23 percent in the 6 to 12 for pediatricians, 40 percent for family practitioners and nurse practitioners 67 percent.

DR. GANLEY: I don't dispute that practitioners, you know, say this. My question is what impact does that have on the consumer when they're seeing an ad or seeing it on a principal display panel of a box. To me, it conveys that this is really an effective therapy and it's really safe. And I think, you know, here I think the question really is how do we get fair balance to that when they're obviously going to get potentially peppered with more advertisements than they are with they are with the education campaign.

DR. SUYDAM: Well, you know, I have to admit that this is not something we discussed in terms of, and came

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to some agreement with the membership about advertising. But I think it's something we will take under advisement and come back to you with some recommendations of how we might change that.

DR. TINETTI: We can advise you to say 75 percent of doctors don't recommend them. That would be one approach.

DR. SUYDAM: Seventy percent of pediatricians.

DR. TINETTI: Pediatricians. Dr. Griffin.

DR. GRIFFIN: Yes, leaving aside the question of efficacy where there seems to be some question about whether that's necessary to have those data for children. It seems like it is necessary to have safety data for children. And I was wondering if FDA thought that the burden of safety data in children is sufficient at this point for children under 6 or children under 12, given that usually some of the problems with the efficacy studies that people have was that the sample size wasn't big enough; and usually you need a bigger sample size for safety than for efficacy. So I'm wondering if we feel like the data on safety is sufficient?

DR. McMAHON: Well, I was going to ask a similar question. Since most of the safety data in children on

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cough and cold products are passive surveillance data, including the poison control data, do we really know how safe appropriate doses of cough and cold medicines, "appropriate" doses of cough and cold medicines are? Actually, specifically referring to what Dr. Rosenthal had asked about subpopulations, potential subpopulations and I would actually ask the panel what the opinion is about that.

DR. GRIFFIN: I guess to follow up, what I saw as far as the clinical trials did not make me feel very secure that I know enough about safety, just having 50 or however many years of use with passive reporting. I don't think that does it for me.

DR. TINETTI: I think there's a pretty overwhelming amount of data, as you know, Dr. Griffin, that randomized controlled trials are not designed for safety. They will never be designed for safety. The numbers will never ever be enough and there's general consensus that the passive reporting isn't as well. It sounds like it's another major gap, I think, in general for FDA, which I think they recognized as well.

Are you going to address this exact point, Dr.

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D'Augustino?

DR. D'AGUSTINO: I designed safety studies with 19,000 subjects in it and we do safety studies routinely now. I don't think the statement you just made is really true. We're designing studies specifically -- randomized controlled trials specifically to look at safety issue. We do that routinely now and I don't see how you can talk about safety if you don't have a sense of the efficacy. I'm not sure I agree with your jump over efficacy. We can't do efficacy, so forget about it. Is it safe? I don't think we should be talking about safety unless we really feel comfortable with the efficacy component. I just don't understand this pK.

Is the FDA saying

DR. TINETTI: Can we hold off on that?

DR. D'AUGUSTINO: Well, no, but it's important.

DR. TINETTI: You're on here. I just want to keep it in order here. So you're on the list on that question.

DR. D'AUGUSTINO: Okay. But we do run big studies on safety.

DR. TINETTI: What's that?

DR. D'AUGUSTINO: We do run big studies on safety.

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DR. TINETTI: And I think that's an important point. My point was that in the usual randomized controlled trial that's looking at efficacy is nowhere near large enough to look at safety, but your point is well taken that it takes much larger and well-designed studies. But we will get back to your other question. Dr. Cnaan, you were next.

DR. CNAAN: Dr. D'Augustino was sort of going in the direction I was going, which is back to the pK. There are 28 approved combinations in the monograph. Are there any plans or discussion to do studies in those by the industry?

DR. SUYDAM: Dr. Gelotte.

DR. GELOTTE: I apologize. Can you repeat your question, please?

DR. CNAAN: Yes, for the 28 combinations that are in the monograph, are there any plans or discussion to do pK studies?

DR. GELOTTE: For the other 28?

DR. CNAAN: The 28.

DR. GELOTTE: For the combos?

DR. CNAAN: I think we saw your plans for six single drugs to do pK studies and I think there wasn't any mention of the combinations. And since these are approved in the monograph, I'm asking about them.

DR. GELOTTE: Okay. Step one is to do these pharmacokinetic studies in children as single ingredients. What we often do in drug development is another type of extrapolation, which is where we look at pharmacokinetic studies in adults, drug interaction studies. We are aware of at least maybe six or seven pharmacokinetic studies in adults with the various ingredients that have not shown drug/drug interactions.

So that gives us at least some information about drug information that could be extrapolated for children and we have done at least pseudophedrine and chlorpheniramine and ibuprofen in the products that were submitted to the agency for NDA and those pK studies had the three or two active ingredients in children and showed no drug interactions.

But again, the starting point would be the single ingredient and then, again, looking at what's in adults and what else that may need to occur as we broaden the research plan.

DR. TINETTI: Dr. Goldstein.

DR. GOLDSTEIN: Resonating to Dr. Tinetti's earlier comment about there aren't enough numbers, I would remind the panel of the numbers that I alluded to this morning, 5.8 billion doses are most of them or many of them, at least, repurchases are done by largely intelligent people and that means something. That's a comment.

The other question I have or question to Dr. Suydam is this. There have been flashes all day of discussion about the education program and the cultural aspects of it and all good and important questions and allusions to advertising and so on, and yet as an emeritus fellow of the Academy, I find that with 62,000 pediatricians in the ranks, I was struck this morning by the absence of the American Academy of Pediatrics from the list of collaborating organizations for the industry with the industry's pediatric initiative while the family practitioner, society and others are visibly present. And

I wonder, Dr. Suydam, can you shed any light on this issue?

DR. SUYDAM: We very much hope that we will be able to have a partnership with the American Academy of Pediatrics in our education program. They were not comfortable right now agreeing to that. I think they wanted to see the outcome of this meeting, but I think it will it's absolutely critical that we have them as a partner and we feel that it's extremely important. They will be great partners, and we have a long history of doing educational program and we have a commitment to that educational program.

We have done things such as child resistant tampering and tamper-evident packaging and we have gone back with our Council on Family Health and the work we've done with the National Council on Patient Information and Education and our current foundation, the Consumer Health Education Center, and we have partnered with many organization and we hope that we will continue those partnerships in this initiative and that the AAP will be one of those partners.

DR. TINETTI: Dr. Shrank.

DR. SHRANK: Thanks. I wanted to push the safety issue a little further, and this is to the FDA. The ERS data seem to be a critical piece of the picture here and I think you did an excellent job of describing the limitations of that dataset and that it offers more of a signal of a problem rather than some sort of quantification of the frequency of the problem.

Have you ever tried to validate that database to get a better sense of how much under reporting there really is? And a second related question, Dr. Kuffner used one of those databases and tried to really parse it out and identify specific episode and I wondered if you thought that the quality of the data is sufficient to be able to do that in a meaningful way and to attenuate the signal that you picked up?

DR. MCMAHON: I am not aware of data -- maybe someone is behind me on validating or comparing errors specifically to safety studies that were done with the denominator. I am aware of such data for VAERS, also used

at the FDA, Vaccine Adverse Event Reporting System, and in that instance there was an article that was very interesting back in the '90s looking at various different vaccine adverse event pairs and with what efficiency they were reported, these adverse vaccine events pairs were reported to VAERS.

And what was found was that it varied a whole lot

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depending on the vaccine adverse event pair, depending on such issues and of course, speculation is there regarding exactly what it depends on, but there were issues such as publicity having been given to particular events with an association to a particular vaccine and that the speculation was that there was more efficiency in those instances. But also that the seriousness of the event seemed to play a big role in the higher efficiencies of reporting to the passive surveillance system and that was the experience from VARES. I'm not sure if anyone behind has such data.

DR. BRINKER: Yes, I'll speak to that. Hi. My name is Allen Brinker. I'm a medical officer and epidemiologist with DDRE. And along with one of my colleagues, we looked into this quantitative question about the numbers and speaking now specifically to AERS, you know, kind of the dumb number that people like to say is that 1 to 2 percent of reports are picked up through Mid Watch, but you know the real answer is that we don't know.

And as my colleagues have said, we think that notoriety and publicity and marketing make a lot of

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difference in reporting. So there's a lot of reason to believe that the numbers that we see in ERS are very, very small.

Now, with regard to the bigger question is how this happens you know, how frequently this happens in the real world, our initial plan to study this question involved looking at the DAWN database, which has just recently been revised and we hoped that that would have given us some really nice insight, not to discredit the poison control database, but we were looking to the DAWN database. We thought that would give us a better

DR. TINETTI: Can you tell us what the DAWN database

system is?
DR. BRINK: Yes, the DAWN database I think is from Samsung and DAWN is Drug Abuse Warning Network, which is what it was five, ten years ago and they've not redeveloped that, which is now instead of just use and abuse of drugs now they're looking at all adverse events, which is going to get us poisonings and drug rashes.
Now, the problem is that that's coming online and they had a problem, a data problem that they realized this past summer and so we were unable to do that analysis.

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We'll get there. So my hope is that we'll have a better quantitative estimate or at least some estimates to compare to the numbers that we get from Poison Control in the near future.
DR. McMAHON: Does that answer your questions, both questions?
DR. SHRANK: Not the second one.
DR. McMAHON: Okay, the second one could you repeat it?
DR. SHRANK: Do you think that Dr. Kuffner really parsed out specific events in one of the databases and I was trying to get a better sense of whether the quality of the data is sufficient to be able to really retrospectively go back and reevaluate to determine which are real and which are not real.
DR. McMAHON: Real meaning?
DR. SHRANK: Serious.
DR. McMAHON: Causally associated or real meaning serious?
DR. SHRANK: I think it's probably serious and/or causal.
DR. McMAHON: The quality of the data in ERS varies

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a whole lot, so there are some reports that have very little data in them and others that are quite detailed. So I think it really varies. Now, we do go through and analyze case-by-case and did do so for this, so there's a lot more granular data than maybe was on all the slides.
DR. TINETTI: Maybe I can ask a follow-up question. Do you think the presentation that was given was it reasonable interpretation of the ERS that was given by industry? Do you think it was a reasonable interpretation

of the data?
DR. McMAHON: I think that was a different database.
DR. SUYDAM: The database that Dr. Kuffner used was the industry database for serious events that McNeil has and has maintained for the last 27 years. What was done at the Rocky Mountain Poison Control Center was to look at all of the fatalities across all the databases, including the ERS death cases. So that included a variety of sources and the analysis you saw from Dr. Dart was based on that.
DR. TINETTI: Dr. Calhoun.
DR. CALHOUN: Thank you. My question is actually for Dr. Akhavan-Toyserkani and I apologize for having

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mispronounced your name, I'm sure.
The question is related to the ERS serious AEs in kids. For cardiac and depressed level of consciousness and respiratory AEs, the frequency of those SAEs was higher in overdoses than in therapeutic doses, but for convulsions it was not the case. And in fact, there was no agent-specific variation in that. It was for all of the agents that you listed that therapeutic doses were more likely to be associated with convulsions
And so that raises a question of whether there is febrile seizure ad mixture in this database and the question then is can that be sorted out by looking at the indication for which the drug was prescribed? If it was for cough and cold with fever and there might have been febrile seizure ad mixture, can you separate that from that same agent given for allergic rhinitis, for example?
DR. AKHAVAN-TOYSERKANI: We did note convulsions in some of the cases and fever was reported. So we do acknowledge that these cases are confounded. However, we did note that they occurred more in the 2- to 5-year age group. The reason why you see them across all the different drugs is that because we're looking at

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combination products and so the same case may have been picked up under each drug since we're dealing with combination products.
DR. CALHOUN: So the question for the other outcomes is, is the potential for ad mixture there that may be confounding our estimates of what the serious AE rate

actually is?
DR. AKHAVAN-TOYSERKANI: I'm sorry. Can you repeat that question?
DR. CALHOUN: Are there ad mixture concerns about the other outcomes like cardiac adverse events and depressed level of consciousness and respiratory adverse events?
DR. AKHAVAN-TOYSERKANI: That's correct. We tried to assess each drug individually and so basically, for all adverse events, because we're looking at combination products. They could have been picked up under each different drug. So it could be the same case coming up under a different drug. That's correct.
DR. CALHOUN: Okay, thank you.
DR. TINETTI: Ms. Hewitt.
MS. HEWITT: Yes, my question is to either the

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petitioners and/or industry. Has anyone given any thought to the impact to "consult a doctor" will have on those individuals in the United States who are uninsured? What educational initiatives are planned to cover that group of the population?
DR. SUYDAM: The statement "consult a doctor," "ask a doctor" is already on the label for all products for children under the age of 2 and for the antihistamines under the age of 6.
MS. HEWITT: I understand that, but in terms of not being able to access a doctor, do you feel that there will be a greater impact on emergency room admissions or emergency room appointments as a result of that?
DR. SUYDAM: Do you mean if the products are not available? I don't really know the answer to that.
DR. SHARFSTEIN: I could maybe just give, you know, from my perspective as a clinician having worked at Children's National Medical Center in the emergency department and seen a lot of uninsured patients. I've taken care of patients with serious complications like Dr. Levy alluded to pneumonia, asthma who were uninsured and thought they were getting by, by taking these medicines,

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by not seeing a doctor.
The parents will when they know that they're going to be getting a big bill, they'll try anything before

some parents will go through whatever they think and if they see a product that says "doctor recommended" and meanwhile their child's getting worse and worse and worse and worse and I've seen some very sad cases where parents just felt horribly guilty because they did not bring their kids in earlier.

We have a lot of uninsured patients in Baltimore City and I want them to be reaching out to all of our clinics where they can get care for free instead of thinking that they can do something for their child at home that may be prolonging the need for very important medical care.

DR. TINETTI: Dr. D'Augustino.

DR. D'AUGUSTINO: I'd like to go back to the efficacy in testing and just try to get an answer which I'm just a simple statistician, so the answer may already be on the table and I just don't understand it. But we're talking about efficacy and we're talking about safety. I think efficacy really has to come before the safety

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issues. You don't expose people to safety issues if there's no efficacy.

Are we saying or are we being told that you can't run an efficacy study from 2- to 6-year-old children?

DR. SUYDAM: No, not at all.

DR. D'AUGUSTINO: Not at all, so why don't we have the sponsor saying, rather than all this pK material and so forth, why don't we rush to put efficacy studies together.

DR. SUYDAM: I think Dr. Walson will respond to that.

DR. WALSON: Yes, although I hope I have time to comment on the alternative to the clinical opinion because I have a different view of children I've treated who were treated with the alternatives. Slide on, first.

(Slide)

DR. WALSON: I think that the first thing is that pK studies were presented as first because they're the first part of an efficacy study. That is, we need to make sure that when we do those efficacy studies in children we use doses that mimic the exposure in adults. So they weren't being presented, as that's all we're going to do. It's

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that we have to do those first because the dose is the first part of an efficacy study.

Now, the next step, I think, was brought up both by Dr. Snodgrass as well as you and others. We need some validated end points. That doesn't mean necessarily that they're the same end points, but we need some things that have been looked at. In general in pediatric studies, we start with 12 and above, make sure it works and then 6 to 12 and they're semi-artificial age breaks, but that's sort of the way drug development goes because you start with the older kids where the safety of doing the study is a little better.

Anyway, these are some examples of medication-specific or even in this case, combination-specific end points, and pharmadynamic end points versus I'll just go over one of them. For example, Capitan (phonetic) induced cough is not yet accepted by the FDA as a measure. It's actually been proposed for some NDA products.

It's actually been studied by Dr. Chang in over 500 children. And it actually looks, at least now, this is again I'm sorry that it's unpublished data and I don't

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have slides to show you. But at least what we've been told from her is that the results are generally similar to adults and we know that, for example, for Guaifenesin that cough frequency in a Guaifenesin/ dextromethorphan combination is very easy to demonstrate in adults with that model.

Now, that model is not accepted for adults either by the FDA, but the point is that there are people already working on what kind of pharmodynamic measures could be used to do the kind of comparison that Dr. Snodgrass said, you know, is the concentration effects similar in a 6-year-old to a 12-year-old? Is it dissimilar? Those are the kinds of things we have to do and there are some other examples in there like mucus.

But one other example I wanted to talk about just because they might be very good scientifically, but you also have to be able to do them. And those of you who are parents here will realize it looks very good to say mucus weight until I tell you all you have to do is have your child blow their nose. And those of you who have tried to

teach your children to blow their nose that's not simple. So we're working on it, but it's not ready for primetime.

DR. D'AUGUSTINO: So we're talking pK studies for dose. We're talking about pediatric end points and validated and we're talking clinical trials.

DR. SUYDAM: Right, yes.

DR. D'AUGUSTINO: And another comment about this education and so forth. I think all you have to do is read the transcripts of previous INDAC meetings. Every sponsor that comes up promises to have an education program and a hard line and so forth, and I don't know where those things go. I mean they probably do and they probably work out very well, and here it's obviously a lot of education that's needed. But I think we'd feel a lot more comfortable if we knew that they had efficacy effective trials and safe doses and so forth.

DR. SUYDAM: If I could comment on that. We have a commitment to doing this education study. We've done education programs in the past. We've partnered with the FDS on many of our education programs. So this isn't something that we're saying just to say in this meeting. We are saying we are going to do this education program.

DR. D'AUGUSTINO: No, I didn't mean to be so flip about the way it came out is that that's always part of

the package, I think, when you, in particular, come and the industry comes and how they work out is very important. But it's something that I don't think we I never remember anybody saying on a panel, well, two years ago a drug we approved, nicotine patches and there was a big education program how did the education program work out?

DR. SUYDAM: We'll be happy to come back and talk to you, particularly about nicotine patches and how they worked out because it's been very good.

DR. D'AUGUSTINO: Exactly.

DR. SUYDAM: And we would be glad to two years from now and talk to you about how our education program has worked out as well.

DR. TINETTI: And you'll tell us how the efficacy studies are coming along, too.

(Laughter)

DR. SUYDAM: Yes, we will, absolutely, and the safety study.

DR. TINETTI: Thank you. Dr. Daum.

DR. DAUM: This is a comment. I guess quite a gap between flagging my hand and getting called on. It's

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occurred to me then, thinking about these efficacy studies, and I know the point has been alluded to a little bit, is that rhinitis has multiple causes and that the drugs may not perform against all causes of rhinitis that you wish to test.

And someone made the comment that the viruses in children and adults are the same and I didn't come to give a thorough review of that subject, but it occurs to me that that's probably not true. That RSV is one good example of something that's extremely different between children and adults. Melanomas virus might be the same. The occurrence of croup might be another difference. Pertussis particularly in its mild form might be another difference as well, although the data are sort of missing about that. But it strikes me that there are very different causes in children than in adults, although a lot of overlap, too. And I really find myself trying to design an efficacy trial and having a hard time thinking about how to do it.

So maybe you could share your since you've obviously begun thinking about it, maybe even started the trials, tell us how you've approached that part of the

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problem and where it goes to extrapolating from adults to children.

DR. SUYDAM: I'd like to ask Dr. Walson to speak to that.

DR. WALSON: Well, I wish I could tell you we're done designing

DR. DAUM: Excuse me. Before you answer, are you doing the trial?

DR. SUYDAM: No.

DR. WALSON: No.

DR. DAUM: Are you designing them?

DR. WALSON: Well, I'm consulting on designing them. There have been researchers I mentioned one there are others working with various sponsors who have been working

on this problem for a long time. While the viruses may be different, and they're certainly different first exposure versus repetitive exposure, et cetera, the basic physiology of how the virus evades the cell and what the cell does to it is similar. How similar is what you're being asked to judge.

But your comment is a good one. That is, are you taking all comers, you know all viral things or are you

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excluding RSV? For example, you mentioned Pertussis, obviously, not a viral infection, but the earlier studies, which were actually done with Pertussis is one of the easiest things to show efficacy. Why that is, I don't know. But if you got a lot of Pertussis or Para-Pertussis in your population might be different. If you don't exclude children with allergic disease, you're more likely to show an effect. But half this group would probably say we want you to exclude allergic disease because we don't want it confounded. The other group would say we want you to put them in because that's the general population that uses the products. We want to know what the general population is. So it's not so easy, but some of the studies with induced cough really can go.

There are some studies I'll put the slide up, but it's just to show you where some studies have done slide on.

(Slide)

DR. WALSON: For example, we mentioned that histamine has a similar response, histamine receptors, et cetera, and we know that a certain number of viruses do release histamine and that's at least part of their

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mechanism of making people miserable. And so one of the things you could do is not have it as admission criteria, but you could look at as a covariant. That is, you could do viral swabs at the onset of disease.

You're going to have to get the kids very early. That's going to require you to recruit them before they get their illness. You're going to probably have to do we do some studies with viral shedding in Cincinnati not me personally, but our infectious disease group where you have a pretty good idea of what's in the community and you'd have good idea of when you wanted to start and stop.

So we're getting some things. Let's have slide on.

(Slide)

DR. WALSON: This is also a slide on also about some of the stuff that's been learned about viruses and colds and some of the articles if you want. They actually have been some interesting studies where people looked at interferon mixed with some of these products. There's a lot of work going on. But again, this kind of work is in adults.

It's a long way, I think, from kids.

I hope I've answered your question. I don't know.

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DR. DAUM: No, I think my question is much more overarching and broad-reaching than that.

DR. WALSON: How can you be sure that you can extrapolate when you're talking about a big bag of diseases.

DR. DAUM: That's my point.

DR. WALSON: Good question.

DR. TINETTI: Good question. Dr. Joad.

DR. JOAD: Yes, I just wanted to establish what we're extrapolating from with the FDA since that wasn't really part of our packet was to determine whether these classes of drugs are effective in adults and the information that was presented by the industry seem to think that it was, although one of the the Cochran report that they mentioned about coughs said that there was insufficient evidence to say that antitussives were effective in adults.

So I wondered if the FDA could comment. Are we assuming that expectorants and antihistamines and decongestants and antitussives are effective in adults so we can be extrapolating from that or not?

DR. GANLEY: Yes, that's not part of your there's

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an assumption that that data has been reviewed and it's effective. I will note one exception, though. There is another citizens petition in questioning the correctness of the dose of phenylephrine and that's going to go to an advisory committee some time in the future. But that's the only ingredient right now that's under question of whether it is an efficacious dose in adults. But you should assume that there's sufficient efficacy in adults.

DR. TINETTI: Dr. Dure.
DR. DURE: Actually, this goes back to Ms. Hewitt's question because there is an answer to that in the CHPA document that over a 14-year period about 110,000 doctor visits were calculated to be avoided. But that is back to 1989, so I don't know how applicable that is.
DR. GANLEY: I just want to ask a question of Dr. Sharfstein and it goes back to some of the points he raised about delaying the diagnosis and more serious illness. And I think what people have to understand in the OTC world there are essentially many things that could be misdiagnosed by an individual.
To take an example, someone could have a headache and take a pain reliever for the headache and it could

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turn out to be a brain tumor. Or a child could have a fever and the parent gives them, you know, and it may be certainly a viral illness and they give them a fever reducer pain reliever and it reduces the fever. In most of those instances, it does not go on into a serious illness, although on the labeling, for example, on a fever reducer it will give instructions that if the fever is not better in three days you should contact your physician for evaluation.
So I need to get an understanding if there's a need to get efficacy data here and efficacy data is obtained, it sounds like that you've created a standard that is so high that any adverse event that delays the diagnosis here, okay, where an individual used an OTC medicine and it goes on to you know, they turned out to have pneumonia or something that that's just unacceptable and that's the perception that I'm getting from some of your comments. I just need clarification.
DR. SHARFSTEIN: Sure. I can clarify that. I look at it at the public health level, not at an individual level. So it's not so much if one patient misses the diagnosis, but overall what's the effect on the population

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of patients who are using the medicines? So for example, for that asthma is pretty common in kids I this age group. Asthma often presents as cough in this age group. I think it would be interesting and important and certainly relevant to just Dr. Levy and myself antidotal experience

to know how these products intersect with asthma because and this relates, in part, to the efficacy.

If there's not efficacy, what is the potential harm and if you could show that at a population level you are missing significant numbers of you know, you're delaying care for a potentially serious condition in kids, then I think that that's a public health consideration that would have to go into a particular medicine.

And I think that there's a danger, particularly, when you talking about products without evidence of efficacy that if you've got serious illnesses that do occur in this population and if you I would say particularly around the another related point that I would make is that it's very important that it be integrated into the pediatric practice. So when I see patients, fever is obviously a really big thing. A lot of education on fever, all the different symptoms of

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fever, how you deal with it and you're trying to explain the appropriate use of the medicines when it helps, when it doesn't help, when to call.

But for these medicines without effectiveness and with a sort of advertising campaign coming in at just different levels than where you are in clinical practice, it creates the potential that you can't you're your message across, that patients could delay diagnosis and I've seen cases like that, but just antidotal and it makes me raise the public health concern that what you wind up doing is, overall, making the health of the children worse.

DR. GANLEY: I just want to follow up on that. I just need to understand. But if it turns out that there was efficacy data here, are you still suggesting there would be a problem because there's going to be misdiagnosis? And also, and I don't know which background material it was in, is that there were it's estimated that children have six to eight cold a season. And so that's an awful lot of calls to a doctor and that's also a public health issue of whether, you know, the healthcare system can accept that responsibility without

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DR. SHARFSTEIN: So to answer your first question, it would depend on the nature of the efficacy data and the

balance a little bit and what you think you're getting for it because the common cold is not that morbid a condition versus the other conditions. It's a little different.

What was the second thing that you just said? I'm sorry.

DR. GANLEY: It had to do with the number of colds. Do we have an idea of what percentage of those go onto pneumonia that requires some type of intervention because you're essentially saying then, you know, kids start coughing, the parents get upset. They're going to call a health provider if they have access to one. So is the health system equipped to accept, you know, six to eight calls a season without some intervention here if it turns out that the risks for pneumonia is really quite small?

DR. SHARFSTEIN: Two things. First, I'm not saying that I know the answer to this public health question. I'm just saying it's worth consideration. That's all I'm saying on that. And because of my experience and Dr. Levy, we think that it's relevant.

As far as the question, I think the public health

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question, for me, as the health commissioner of Baltimore is whether kids are getting seriously ill. It's not whether pediatricians are too busy. And in fact, what the pediatric community is going to say is we want to hear from parents if they're worried about their kids. We don't want them saying take Dimetapp and don't worry. We want to hear about it.

When I stood up with the nine or I guess there were about five chiefs of pediatrics at a press conference in Baltimore, a city where those guys are working really hard and they have lots of patients coming into the clinic already, to a person they said we want to hear from you. That's why we went into pediatrics. We want parents to call us and eventually develop trust. They don't call for the eight colds. If it's my kids, it's a month. But they don't call all the time, but it's perfectly fine, I think, and certainly in Baltimore the pediatric community has spoken every clearly that we would rather hear, we don't consider it a public health problem to have too many parents calling doctors. We consider it a public health problem that four kids died and the medical examiner said their deaths were associated with these products.

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DR. TINETTI: Dr. Walson.

DR. WALSON: Well, a lot of issues were raised. First, the educational one, which was alluded to, this is an issue of education. Physicians should be discussing the proper use of symptomatic medicines before the children are ill. At least two of the cases presented were not only cases where an education, proper education of your patient should have prevented it, but where the patients were not following the label directions. And so part of the educational campaign will be to educate healthcare providers to you know, how do you teach people to read.

The next thing is the general comment about the public health. Parents will use something. I've seen children die from alternative medicines, psoriasis in a 2-year-iold, for example, given for a cold because the parent didn't believe OTC medicines work. I've seen children seize because they were given a topical camphor-containing product because their grandmother gave it to them and believes that it works for colds. There are already all over the Internet I just saw one during the break every alternative healthcare marketing company

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is out there telling them come to us. They're taking away these products. You can use our crap.

DR. TINETTI: I think the points are well taken, but I think we can have antidotes on both sides and I think we really want to move this on to science and a little bit away from antidotes.

DR. WALSON: But for those products there are not efficacy studies, not just poor efficacy studies. Okay.

DR. TINETTI: I think what we're hearing

DR. WALSON: And no safety data.

DR. TINETTI: And I think we can also say that also there may be a few situations where people delayed. I don't think that's what we're addressing here. I think that's perpherial to our issue. We really haven't made that direction connection, so think I would like the panel to stay focused on what we're actually asked to address here.

I think we may be done unless anybody has any final burning questions. I want to thank you all for your

attention today and all the careful work that went into this and the panel, hopefully, will sleep on all of the issues that were raised and be ready to address them tomorrow. Thank you.

(END OF DAY ONE.)

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I, Gloria Hooker, do hereby certify that this transcript was prepared from tape to the best of my ability.

I am neither counsel nor party to this action nor am I interested in the outcome of this action.

Gloria Hooker

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