Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to FDA Questions

Module 1 of 3

Responses to FDA's Nine Questions Published in the August 25, 2008 Federal Register

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

EXECUTIVE SUMMARY

Introduction

The Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements in the United States, including pediatric cough and cold medicines. As such, CHPA has an interest and expertise in responding to the request by the Food and Drug Administration (FDA) for comments on nine questions published in the *Federal Register* on August 25, 2008, to obtain public comment about certain scientific, regulatory, and product use issues as it proceeds with the rulemaking and reviews new drug applications (NDAs) for ingredients marketed in OTC cough and cold drugs marketed for pediatric use [1]. In this submission, the CHPA Pediatric Task Force is providing comments to the nine questions, as well as supplemental information that may be useful for the Agency as rulemaking proceeds.

Position of the CHPA Pediatric Task Force on Cough and Cold Medicines for Pediatric Use

Children's OTC cough and cold medicines are safe and effective when used as directed, and the leading makers of these medicines are committed to working with the FDA and pediatric experts to ensure that parents and caregivers have appropriate treatment choices for their children. The leading manufacturers of oral OTC pediatric cough and cold medicines are moving forward on both the design and implementation of initiatives aimed at encouraging the appropriate use of these medicines. Additionally, in consultation with FDA and outside experts, manufacturers are conducting studies to reaffirm the effectiveness of oral OTC pediatric cough and cold medicines through pharmacokinetic studies to confirm or refine appropriate dosing schedules for children and to reaffirm the effectiveness of these medicines with current and appropriate clinical trial designs.

Background on OTC Cough and Cold Medicines for Pediatric Use

Based on rare patterns of misuse leading to overdose, particularly in infants, the leading makers of OTC cough and cold medicines announced on October 11, 2007 voluntary market withdrawals of oral cough and cold medicines that referred to "infants." Later that same month, FDA convened a joint meeting of the Nonprescription Drugs and Pediatric Advisory Committees to discuss the safety and efficacy of OTC cough and cold products marketed for pediatric use. Among the committee's other recommendations to FDA, the committees supported the industry voluntary action and recommended additional research

be conducted on cough and cold ingredients in children. On January 17, 2008, FDA issued a Public Health Advisory recommending that OTC cough and cold products not be used to treat infants and children under 2 years of age.

On October 7, 2008, after consulting with FDA, the leading manufacturers of OTC pediatric cough and cold medicines announced a voluntary transition of the labeling on oral OTC pediatric cough and cold medicines to state "do not use" in children under four years of age, with the modified labels continuing to provide dosing information for children four and older. In addition, for products containing antihistamines allowed under the FDA OTC Drug monograph, manufacturers are voluntarily adding new language that warns parents not to use antihistamine products to sedate or make a child sleepy. These actions were taken in an abundance of caution as analysis of postmarketing data shows that dosing errors and accidental ingestions—not the safety of the ingredients themselves when properly dosed—are the leading causes of rare adverse events in young children. At the same time as the announcement, CHPA confirmed that, in consultation with FDA and outside experts, manufacturers are conducting studies to reaffirm the effectiveness of oral OTC pediatric cough and cold medicines through pharmacokinetic studies to confirm appropriate dosing schedules for children and to validate the efficacy of these medicines with current and appropriate clinical trial designs.

Overview of CHPA Pediatric Task Force's Submission

This submission provides comments on the nine questions listed in the *Federal Register* notice August 25, 2008; describes a collaborative pediatric research program to further support the safety and efficacy of pediatric cough and cold products; and provides supplemental information that may be useful for the Agency as it proceeds with the rulemaking and reviews new drug applications (NDAs) for ingredients marketed in OTC cough and cold medicines marketed for pediatric use. The submission is organized into three modules:

Module 1: CHPA responses to FDA's nine questions published in the *Federal Register* August 25, 2008

Module 2: Supplemental information for FDA's rulemaking process:

- CHPA briefing book for the October 2007 Advisory Committee
- Data presented at the October 2007 meeting regarding the safety of pediatric cough and cold products (not included in the briefing book)
- Additional data to supplement the October 2007 presentation and briefing book

Module 3: CHPA Educational Program on Oral Pediatric Cough and Cold Medicines

Overview of Key Points in the CHPA Pediatric Task Force's Responses to FDA's Nine Questions (Module 1)

FDA Question 1: "What types of studies, if any, should be conducted to assess effectiveness and/or safety, and determine appropriate dosing of cough and cold ingredients in the pediatric population? How should these studies be designed and powered?"

Children's OTC cough and cold medicines are safe and effective when used as directed. Although there are significant data to show the effectiveness in adults, the data in children are less robust in favor of cough and cold medicines. Pediatric research has evolved over the past 10 years, and thus, the CHPA Pediatric Task Force plans to reaffirm the science supporting the use of eight monograph cough and cold ingredients including brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine and pseudoephedrine.

The industry-sponsored, pediatric research program will confirm or refine labeling for OTC dosing, reaffirm effectiveness, and further support the safety of cough and cold ingredients in children, ages 2 to under 12 years. The plan for each ingredient may differ, although the general approach includes integration and bridging of existing data with new data obtained across study types and populations. The types and numbers of studies will be based on scientific, yet pragmatic, decisions to obtain the best results for children. The overall coordinated pediatric research program will be highly complex, requiring modifications as new information and learnings are obtained, and it will depend on significant guidance from FDA and consultation with experts in pediatric and cough and cold research. Given the program's scope, complexity, and unknowns with regard to measuring symptomatic relief from cough and cold ingredients in children with the common cold and other respiratory conditions, the pediatric research program will be completed in stages over a number of years.

FDA Question 2: "Should cough and cold products for the pediatric population continue to be available OTC, or should they be made available only by prescription?"

Pediatric cough and cold products have been shown to be safe and effective for use in the pediatric population. Analysis of data from years of real-world use demonstrates that serious adverse events are very rare and parents can and do properly recognize and treat their children's colds. Pediatric cough and cold products are appropriate for self-medication and do not meet the criteria to be made available only by prescription. A change to prescription status would present difficult legal and regulatory problems, including the need for an amendment to the relevant final OTC drug monograph and the approval of new drug applications for the affected products. The ultimate resolution for the question raised by FDA from a legal and regulatory perspective should consist of a combination of revised OTC labeling directed to consumers and labeling for healthcare professionals, as has been done for other OTC drugs.

FDA Question 3: "If the pediatric indications and dosing for cough and cold products were no longer available OTC, would the public use the adult formulations of the OTC monograph products for children, and thus create a greater risk of misuse or overdose?"

When used appropriately at recommended doses OTC pediatric cough and cold medicines have a safety and effectiveness profile that is appropriate for OTC use. Without pediatric cough and cold products, there is a risk that parents could turn to either adult formulations of OTC monograph products or other alternatives, the safety and efficacy profiles of which are less well studied and less well documented than those of pediatric OTC cough and cold medicines. Current survey data demonstrate that parents and other caregivers want access to OTC cough and cold products for their children, and therefore, the risk of potential misuse of adult products exists. To minimize these risks, the CHPA Pediatric Task Force has implemented a multiyear education campaign aimed at encouraging the appropriate use of these medicines in accordance with the labels that have voluntarily been changed.

FDA Question 4: "Do the answers to the previous questions depend on the age of the pediatric patients? If so, how should age be considered in making regulatory decisions for these products?"

Age of pediatric patients has been taken into account in the CHPA responses to FDA's questions 1, 2, and 3. Specifically,

- The response to Question 1 regarding types of studies describes a pediatric research program that is age-dependent by design.
- The response to Question 2 regarding the OTC status of pediatric cough and cold medications does not depend on age.
- The response to Question 3 regarding the risk of misuse of adult formulations would not depend on age. Parents and caregivers of children of all age groups could take actions that would result in increased risk. To minimize these risks, CHPA and the companies represented on the CHPA Pediatric Task Force have a multi year education campaign aimed at encouraging the appropriate use of OTC cough and cold medicines.

FDA Question 5: "At the time the monograph was established, FDA routinely extrapolated safety and efficacy data from adults to children age 12 and over. Current PREA standards permit extrapolation of pediatric efficacy -- but not safety—based upon sufficient adult data. Does it remain appropriate to recommend in the cough and cold monograph that children 12 and over should receive the same dose of medication as adults, without requiring any additional studies in children in this age group? What additional safety and/or efficacy studies should be required in this age group?"

Cough and cold ingredients are regulated under the FDA's OTC monograph system in which doses for children 12 and over are the same as those in adults. Under the industry sponsored pediatric research program, most of the new pharmacokinetic studies will recruit subjects up to 18 years. Where adolescent pharmacokinetic data indicate comparable drug exposure to that in adults at the same dose, then the current OTC indication for the cough and cold ingredient would be supported by available adult effectiveness data. Therefore, additional efficacy studies in this cohort are not necessary. If drug exposure in adolescents is confirmed as comparable to adults at the current monograph dose, then historical pediatric and adolescent safety data is sufficient and safety studies are not needed.

FDA Question 6: "What is the most appropriate method for determining pediatric doses that could be used as an alternative to the quarter- and half-dose assumptions used in the monograph? Should products be dosed by age, by weight, or both?"

To confirm or refine pediatric doses for children 2 to under 12 years, the most appropriate method should be scientifically based, using pharmacokinetic data, models, and/or simulations to guide decisions. Pediatric doses of each OTC ingredient should be based on pediatric pharmacokinetic data that provide adequate drug exposure as that in adults, be linked to adult effectiveness data, and be supported by historical pediatric safety data. Once the pediatric dosing of each ingredient is evaluated and confirmed, OTC labeling for the dosing instructions must be determined. Leading scientific experts in academia and industry believe that label dosing should be first based on weight, and if parents don't know the weight of their child, then they would dose based on age. Importantly, the pragmatic aspects of communicating weight and age for OTC labeling of pediatric doses must be considered, as must harmonized dosing schedules that are compatible with single- and multiple-ingredient pediatric medicines.

FDA Question 7: "There are monographs for topical and intranasal ingredients to treat the common cold. Should these monographs be considered in a similar fashion to the oral cough and cold products? Are the answers to the previous questions different for any subcategories of cough and cold medicines (e.g., topical or intranasal products)?"

Topical and intranasal ingredients should not be considered in a similar manner to orally ingested cough and cold ingredients. Topically administered cough and cold products offer an alternative delivery system direct to the symptomatic organ and demonstrate a lower systemic bioavailability of the active ingredient than orally administered products.

FDA Question 8: "The CCABADP monograph allows for the combination of ingredients to treat colds and/or coughs. Should combination products be permitted for all pediatric age groups? Should data be provided to support each unique combination?"

Children commonly develop acute respiratory tract infections (colds) with one or more symptoms including nasal congestion, cough, runny nose, pain and fever. Caregivers and healthcare providers currently use both single ingredient and combination ingredient products when treating children with colds when one or more symptoms are present. Combinations of pediatric cough and cold ingredients should remain available for children ages 4 and older because they address the need for treatment of simultaneous cold symptoms and have the potential to reduce the number of dosing errors. In the course of the pediatric research program, it is unnecessary to confirm safety and efficacy of every combination product when scientific data are available for the individual ingredients in children or adults consistent with FDA's OTC combination drug policy.

FDA Question 9: "Can measurement errors in dosing be reduced using more standardized measuring devices or alternative dosage forms and, if so, what is the best way to effect this change?"

The leading manufacturers of children's OTC cough and cold medicines are committed to working with FDA, the Center for Disease Control (CDC) and pediatric experts to ensure that parents and caregivers have appropriate treatment choices for children, accurate tools with which to administer medications to limiting dosing errors, and child-resistant packaging to prevent accidental ingestions. To be accurate, measuring devices and alternative dosage forms must be tailored to the physico-chemical characteristics and dosing recommendations of a specific product. There is not one solution for all products, and one standard measuring device would not necessarily reduce measurement errors. Consumer education on the appropriate use of dosing devices and administration may help to decrease medication errors, and some of these elements are incorporated into the current multi year CHPA pediatric education program.

Overview of CHPA Pediatric Task Force's S*upplemental Information for FDA's Rulemaking Process: *(Module 2)

The documents provided in Module 2 include the briefing information and additional presentations for the October 2007 meeting of the Nonprescription Drugs and Pediatric Advisory Committees and other information to address important issues regarding the safety and efficacy of OTC pediatric cough and cold medicines, including antitussives, expectorants, nasal decongestants, antihistamines, and combination products. The CHPA Pediatric Task Force has conducted a review of the available data related to the safety and efficacy of the ingredients available in this category, including market research with caregivers and healthcare professionals who use them. The scientific and other materials included address the following areas:

- Importance and benefits of treating of cough and cold symptoms
- Efficacy of OTC cough and cold medicines in adults and children
- Overview of pharmacokinetics of cough and cold ingredients
- Safety analyses of published and other publicly available data
- Caregiver and healthcare professional insights

It is the Task Force's priority is to ensure that parents and families have access to the best possible OTC medicines available today and that caregivers have the resources and information needed to use these medications safely and appropriately.

Overview of CHPA's Educational Program on Oral Pediatric Cough and Cold Medicines (Module 3)

The CHPA Education program focuses on educating parents and caregivers advising them as follows:

- Follow the dosing recommendations exactly and use the measuring device that comes with the medicine.
- Do not give a medicine only intended for adults to a child.
- Do not use two medicines at the same time that contain the same ingredients.
- Prevent unsupervised ingestions by keeping all medicines out of the reach and sight of children.
- Do not use antihistamine products to make a child sleepy.
- Consult a physician or healthcare professional with questions.

CHPA and its member companies have a long history of educating consumers on the safe use of OTC medicines and have taken the lead on many important initiatives over the years. From child resistant packaging to tamper-evident packaging and the development of the OTC Drug Facts label in conjunction with FDA, CHPA has been proactive and unwavering in its commitment to providing the highest quality medicines to the millions of American families who rely on them each and every day, as well as the disseminating information and tools to use these medicines appropriately. The materials provided in this document reflect the collective work and views of the following CHPA member companies who currently market OTC cough and cold medicines for children and are working together as the CHPA Pediatric Task Force:

McNeil Consumer Healthcare
Novartis Consumer Health, Inc.
Perrigo Company
Prestige Brands, Inc.
The Procter & Gamble Company
Reckitt Benckiser, Inc
Wyeth Consumer Healthcare

Reference

1. Over-the-Counter Cough and Cold Medications for Pediatric Use; Notice of Public Hearing. *Federal Register* 73: 50033-20036 (2008).

Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 1

FDA Question:

"What types of studies, if any, should be conducted to assess effectiveness and/or safety, and determine appropriate dosing of cough and cold ingredients in the pediatric population? How should these studies be designed and powered?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 1

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1 FDA QUESTION 1

"What types of studies, if any, should be conducted to assess effectiveness and/or safety, and determine appropriate dosing of cough and cold ingredients in the pediatric population? How should these studies be designed and powered?"

1.1 Position of the CHPA Pediatric Task Force

Cough and cold ingredients have been made available to consumers through the OTC monograph process. Expert reviews were conducted on the safety, effectiveness, and labeling for each ingredient, resulting in FDA's assessment of these ingredients as generally recognized as safe and effective. Although there are significant data to show the effectiveness in adults, the body of evidence in children is not as robust in favor of cough and cold medicines. While practical experience for many years by both doctors and parents using these medicines demonstrates that these ingredients are effective in relieving cough and cold symptoms in children, the CHPA Pediatric Task Force intends to reaffirm the science supporting eight monograph ingredients. Our position in response to Question 1 follows:

- To determine appropriate dosing and reaffirm effectiveness and/or safety of cough and cold ingredients in children, ages 2 to under 12 years, the pediatric research program sponsored by industry should
    - integrate and bridge existing data with new data obtained across study types and populations; and
    - be based on scientific, yet pragmatic, decisions with regard to types and number of studies to obtain the best results for children.
- The designs and power of new efficacy studies should
    - have endpoints that align with pharmacological effects, map to indications permitted by the OTC Monographs, and are tailored to children;
    - consider the challenges and opportunities associated with evaluating symptom relief in the natural cold model; and
    - consider the challenges and opportunities associated with pediatric studies, while acknowledging advances in pediatric research.

- The overall pediatric research program will be
    - highly complex, requiring modifications as new information and learnings are obtained;
    - dependent on significant guidance from FDA, consultation with experts in pediatric and cough or cold research, and cooperation among companies on the CHPA Pediatric Task Force; and
    - completed in stages over a number of years because of its scope, complexity, and unknowns with regard to measuring symptom relief of cough and cold ingredients in children with the common cold or other respiratory conditions.

1.2 Pediatric Research Program

1.2.1 Objectives

The three main objectives of the pediatric research program on eight cough and cold monograph ingredients are (1) to confirm or refine appropriate pediatric OTC doses, (2) to reaffirm pediatric effectiveness in treating symptoms, and (3) to further support pediatric safety.

1.2.2 Integrate and Bridge Existing Data with New Data

The industry-sponsored, pediatric research program on OTC cough and cold ingredients in children, ages 2 to under 12 years, will be designed to integrate and bridge existing data with new data. The eight ingredients to be studies are listed in Table 1-1 by therapeutic class, and the types of existing data and new data that would comprise the research program can be sorted into at least eleven categories listed in Table 1.2. For example, the types of existing data needed to guide decisions and design future studies include data that are relevant to the progression of cold signs and symptoms, and data on instruments and endpoints that can measure treatment-related changes in symptoms of the common cold, allergic rhinitis, and other respiratory conditions. In addition, historical data on pharmacokinetics, adult doses and effectiveness, and pediatric safety as they pertain to the indications permitted by the OTC Cough and Cold Monograph will be considered. Importantly, these existing and historical data will provide the framework to obtain new pediatric data generated from a selection of pharmacokinetic, exploratory endpoint, pharmacodynamic, and placebo-controlled efficacy studies that will be designed with input from experts from industry, FDA, and academic research institutions.

Table 1-1. OTC Cough and Cold Ingredients Included in the Research Program

Antihistamines		Nasal Decongestant (Oral)
Brompheniramine	*Chlorpheniramine*	*Phenylephrine*
Diphenhydramine	*Doxylamine*	*Pseudoephedrine*
Cough Suppressants		Expectorant
Dextromethorphan		*Guaifenesin*
Diphenhydramine		

Table 1.2 Categories of Data or Information that would Support the Pediatric Research Program of OTC Cough and Cold Ingredients

A. Historical Data on Adult Doses and Effectiveness
B. Historical and New, Adult and Pediatric Pharmacokinetic Data
C. Historical Pediatric Safety Data
D. Pharmacokinetic Modeling and Simulation of Doses
E. Consumer Understanding of Dosing Directions and Devices
F. Indications in the OTC Cough and Cold Monographs
G. Existing Data on Pharmacological Response
H. Data on Progression of Signs and Symptoms Due to Colds and Respiratory Conditions[a]
I. Data on Instruments and Endpoints for Signs and Symptoms Due to Colds and Respiratory Conditions[a]
J. New Pediatric Effectiveness and Pharmacodynamics Data
K. Scientific and Pragmatic Considerations Regarding Links, Bridging, and Execution

a: respiratory conditions include allergies, hay fever, chest congestion, and bronchitis

1.2.3 High-Level Road Map

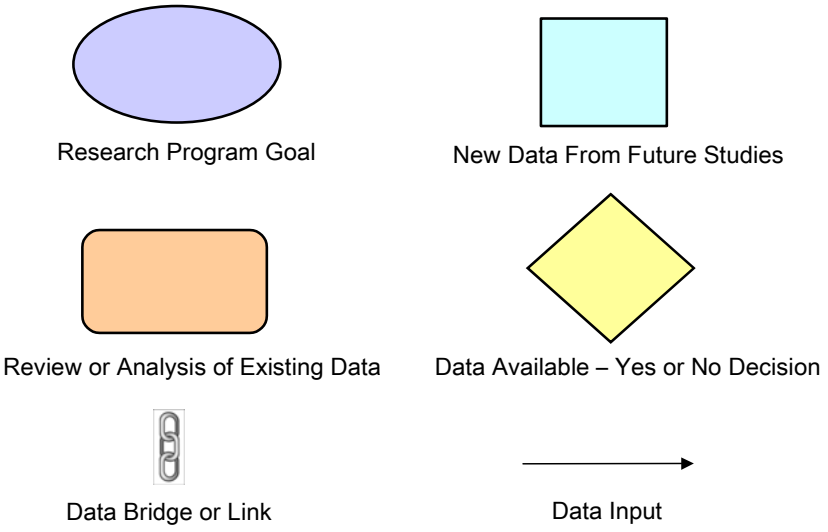
Given the scope and anticipated complexity of an industry-sponsored pediatric research program, we have assembled the decision points, historical data sources, and potential new studies into a generic research plan consisting of three schemes. This road map is a starting point based on current thinking, and does not represent industry commitments for specific types and number of studies for each ingredient. It is intended to facilitate ongoing discussions among companies of the CHPA Pediatric Task Force, divisions of FDA, and academic research experts. As new information and learnings are obtained, the pediatric research program, which is intended to support the OTC Cough and Cold Monographs, will continue to evolve and require modifications.

Schemes 1, 2, and 3 of the generic research plan organize existing, historical, and new data that could support the three main objectives of the pediatric research program, namely, to confirm or refine pediatric doses, to reaffirm effectiveness, and to support safety, respectively. The types and amount of historical data available differ for each therapeutic class, in general, and for each ingredient. Therefore, depending on the therapeutic class or ingredient, Scheme 2 (to reaffirm pediatric effectiveness) outlines a research approach that either primarily

- integrates existing or historical data with new pediatric pharmacokinetic and effectiveness data (Scheme 2A), or
- bridges historical effectiveness data with new pharmacokinetic and/or pharmacodynamic data (Scheme 2B) as discussed in Section 1.3.2.

These schemes are briefly described in the following sections.

Symbol Key for Schemes 1, 2, and 3:



1.3 Scientific and Pragmatic Decisions Regarding Types and Number of Studies

Schemes 1, 2A, 2B, and 3 may be used as general guides to outline the types of studies that may comprise the industry-sponsored, pediatric research program. The types and number of studies, as well as the approach (e.g., order of studies and pediatric age groups enrolled) may differ for each cough and cold ingredient, because they will be based on available data and other important scientific and pragmatic considerations to obtain the best results for children.

1.3.1 Pediatric Pharmacokinetic Studies and Appropriate Pediatric OTC Doses

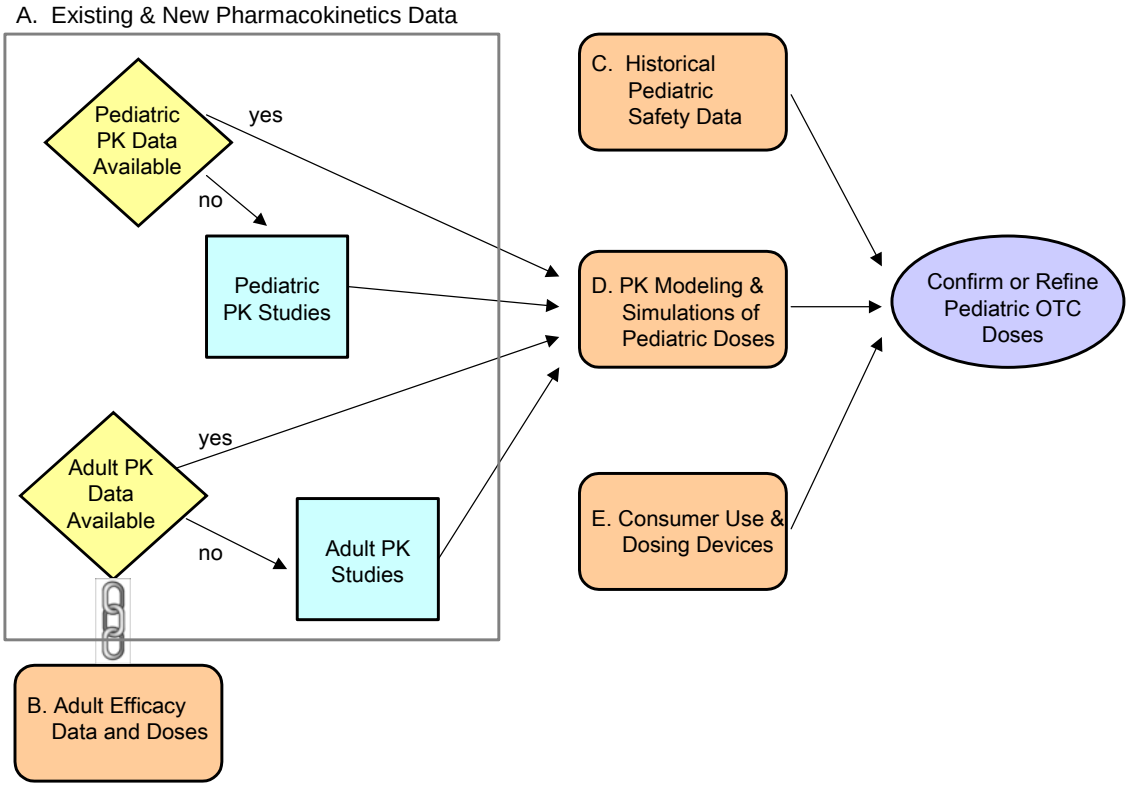
The CHPA Pediatric Task Force plans to use the current pediatric OTC doses in future efficacy assessments if they are confirmed using pediatric pharmacokinetic data, models, and/or simulation techniques. However, where necessary, the pediatric doses may be refined within the framework of the monograph.

Scheme 1 outlines data and pathways to confirm or refine pediatric OTC doses for the eight ingredients. The first step is the review of historical pharmacokinetic data in adults and children. As presented by CPHA at the October 2007, FDA Advisory Committee Meeting on Pediatric Cough and Cold Medicines [1], extensive pharmacokinetic data are available for pseudoephedrine in children, ages 2 to under 12 years, from four pediatric studies. Pharmacokinetic data are also available for chlorpheniramine in older children, ages 6 to under 12 years. For the other ingredients lacking such data, the CHPA Pediatric Task Force has committed to conduct seven single-dose pediatric pharmacokinetic studies, which have been planned or are underway recruiting children.

Historical pharmacokinetic data in adults from one or more studies may be pooled with pediatric pharmacokinetic data in a modeling and simulation analysis to explore a range of appropriate pediatric doses and dosing intervals [2]. Where pharmacokinetic data for these cough and cold ingredients exist in adults, there is no need to conduct additional adult pharmacokinetic studies for comparison of systemic exposures.

As shown in Scheme 1, new pediatric and historical adult pharmacokinetic data will be pooled under a pharmacokinetic analysis plan. The first objective of this plan would be to describe the pharmacokinetics of the cough or cold ingredient after oral administration in children and adults, including the influence of subject covariates (e.g., age and body weight) on the intersubject variability. The second objective would be to assess the current pediatric OTC dosing schedules using pharmacokinetic models and/or simulation techniques. These will help identify potential dosing rules in children that provide a distribution of systemic exposures comparable to those observed for the adult dose and multiple-dose regimen associated with efficacy.

Scheme 1. Integrate Historical and New Data to Confirm or Refine Pediatric Doses



In addition to the results of the modeling and simulations, other inputs into the selection of pediatric doses include historical safety data in children and the pragmatic aspects of OTC dosing, namely, ease of consumer understanding and suitability for single- and multiple-ingredient medicines.

In summary, the strategy for assessing the adequacy of different OTC pediatric dosing schedules for children, ages 2 to under 12 years, will be based on overall consideration of

- drug disposition
- number of weight-age divisions
- single- and multiple-dose drug exposure
- dosing interval
- ranges of systemic exposure associated with adult efficacy and safety
- pediatric safety data
- pragmatic aspects of OTC dosing

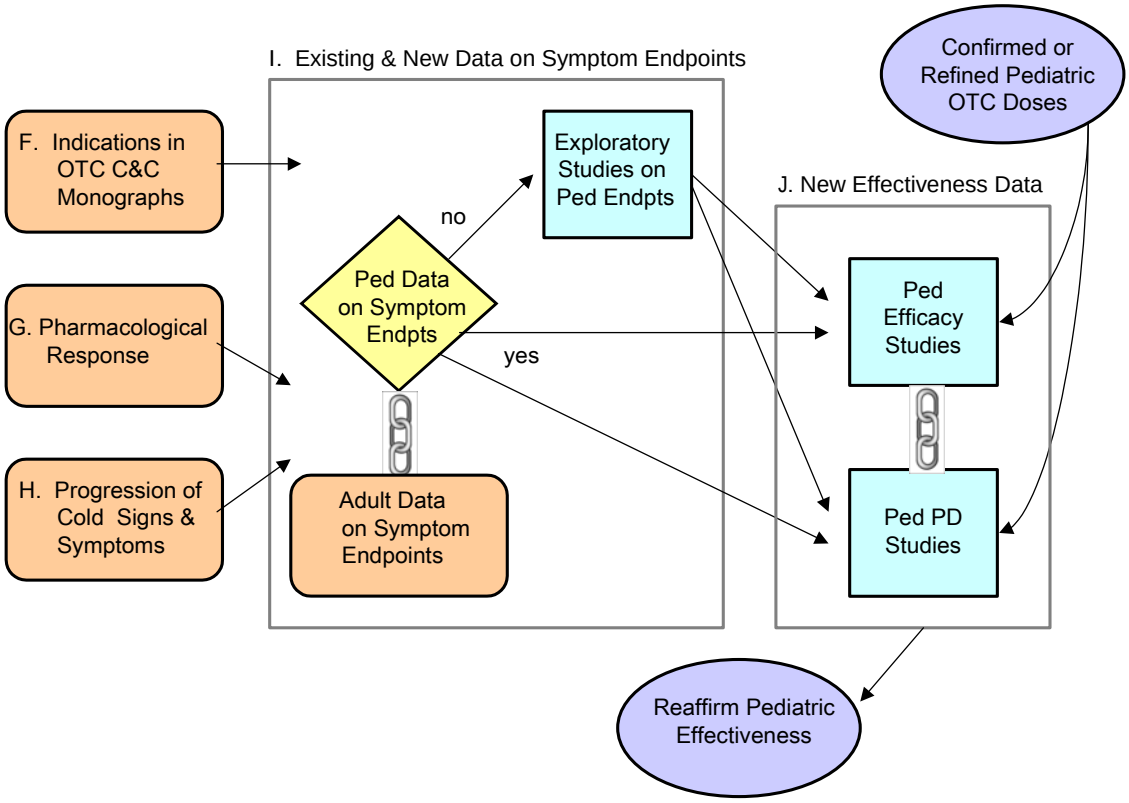
Further details regarding Scheme 1 to confirm or refine pediatric OTC doses are provided in this submission as part of the response to FDA's Question 6 on methods to determine appropriate pediatric dosing.

1.3.2 Pediatric Efficacy and Pharmacodynamic Studies to Reaffirm Effectiveness

For OTC monograph ingredients, "Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed [CFR 21: 330.10(4)(ii)]." Schemes 2A and 2B outline valid pathways to reaffirm effectiveness of cough and cold ingredients in children either by the integration of existing and new pediatric data, or through bridging historical and new pediatric data. The approach will depend on the ingredient and age group being studied, and on its scientific merit and feasibility. In both schemes, future pediatric clinical efficacy and pharmacodynamic studies will be designed to support indications in the OTC Cough and Cold Monograph with an understanding of the ingredient's pharmacological effects and the progression of signs and symptoms.

As highlighted in Scheme 2A, the CHPA Pediatric Task Force has begun a comprehensive review of objective and subjective, instruments and endpoints that have been used in adult and pediatric efficacy studies of drugs that treat symptoms associated with the common cold and other respiratory conditions, including chest congestion.

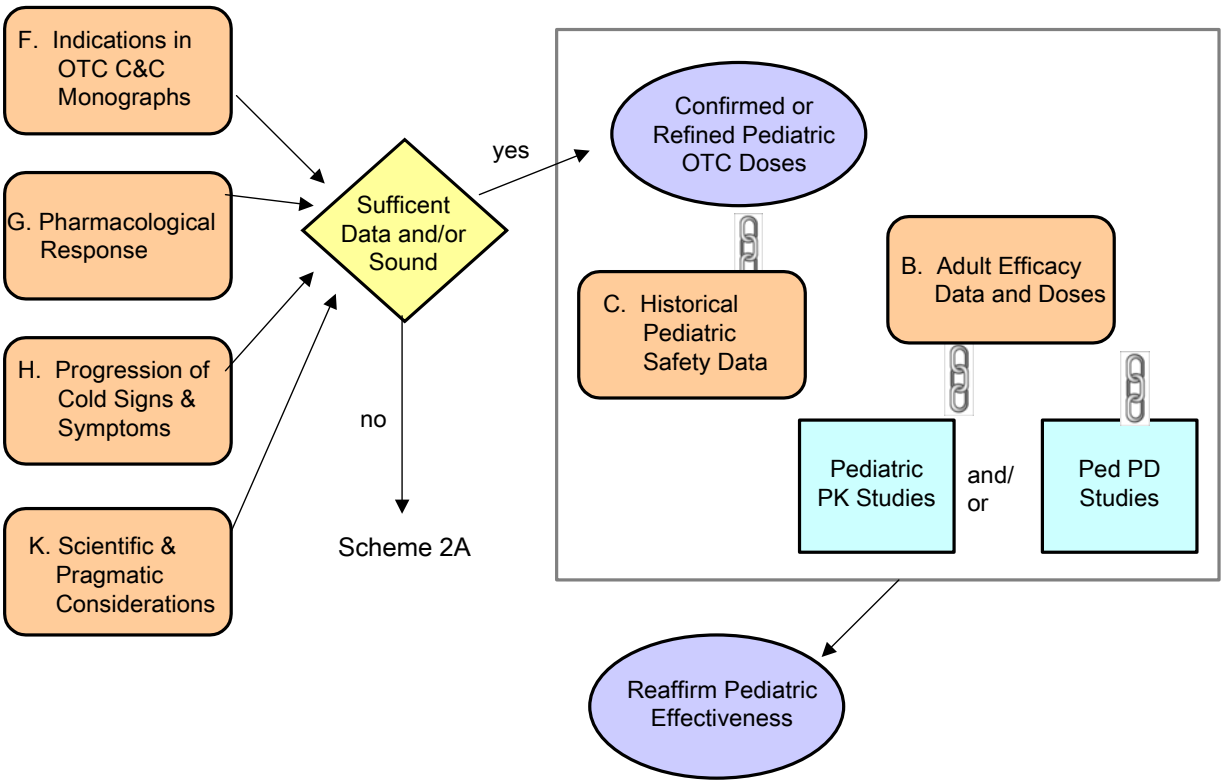
Scheme 2A. Integrate Existing and New Data to Reaffirm Pediatric Effectiveness



As part of the assessment of instruments and endpoints, academic experts in pediatric clinical research and those who conduct research in the common cold and allergies will be consulted. Where there might be sufficient evidence for sensitivity and reliability in measuring changes in signs or symptoms with drug treatment in children, those instruments and endpoints will be considered for a future pediatric efficacy or pharmacodynamic study. Otherwise an exploratory study would be considered where there might be a need to evaluate or adapt possible instruments or endpoints for children.

Scheme 2B allows for potential opportunities to bridge historical adult effectiveness data and related pediatric effectiveness and pharmacokinetic data among the ingredients and children's age groups. It may not be necessary to reaffirm effectiveness of all four antihistamines (relief of rhinorrhea and sneezing) or feasible in younger children.

Scheme 2B. <u>Bridge</u> Historical and New Data to Reaffirm Pediatric Effectiveness



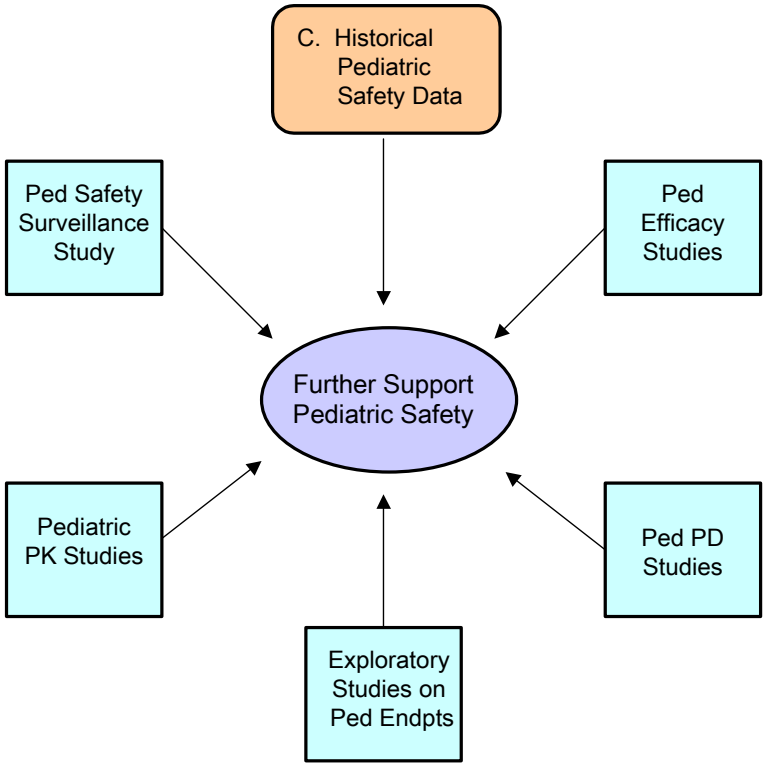
Furthermore, available effectiveness data for ingredients with similar therapeutic uses in different disease conditions can be supportive through bridging. For example, pediatric data for the relief of nasal congestion by pseudoephedrine in upper respiratory allergies are relevant to the same symptom relief in the common cold. Likewise, pediatric data for the thinning of mucus associated with chest congestion in bronchitis by guaifenesin are relevant to the thinning of mucus in the common cold. Under FDA's Effectiveness

Guidance [3], clinical evidence for effectiveness does include experience with the drug or others in its therapeutic class, in the disease or condition, or in related diseases or conditions. The decision to use an approach outlined by Scheme 2B will be based on scientific and pragmatic considerations, as highlighted above, as well as on emerging pediatric effectiveness data and other information that becomes available from exploratory studies on the feasibility and sensitivity of endpoints in younger and older children.

1.3.3 Historical and New Pediatric Safety Data to Further Support Safety

Scheme 3 captures the sources of historical and new pediatric safety data that will further support the safety of each cough and cold ingredient. Historical pediatric data will include comprehensive reviews of safety information from published and unpublished clinical studies in children and post-marketing adverse event databases. New pediatric safety data will be collected and reviewed during all pharmacokinetic and efficacy studies that comprise the industry-sponsored, pediatric research program. For example, adverse events will be monitored during these studies, and depending on the safety profile of the ingredient, other safety assessments (e.g., blood pressure, heart rate) may be considered as needed. In addition, the CHPA Pediatric Task Force is sponsoring a safety surveillance program of cough and cold ingredients in children through the Rocky Mountain Poison Center in Denver, Colorado.

Scheme 3. Integrate Historical and New Data to Further Support Pediatric Safety



1.4 Study Design Considerations

1.4.1 Selection of Doses for Efficacy Studies

1.4.1.1 Based on Pharmacokinetic Data and Pragmatic Considerations

The CPHA Pediatric Task Force plans to use the current pediatric OTC doses in future efficacy studies where they are confirmed to be appropriate using pharmacokinetic modeling and/or simulation techniques. However, where necessary, the pediatric OTC doses may be refined within the framework of the monograph. One approach may be to reaffirm the effectiveness of a current pediatric OTC dose at one of two dosing intervals that are permitted by the Cough and Cold Monograph. For example, the pharmacokinetic modeling and simulations may show that the distribution of systemic exposures would be comparable at the current OTC dose if they were given every 4 hours in children and every 6 hours in adults. Alternatively, the distribution of systemic exposures may be comparable at the higher of two permitted pediatric doses, where applicable.

Another potential refinement in a dosing schedule may be the inclusion of doses for a greater number of weight-age divisions such that children from 2 to under 12 years old will receive a consistent range of "mg/kg**"** doses. Pharmacokinetic modeling and simulations would explore different numbers of divisions to provide a distribution of systemic exposures across age groups, including adults, that would be supported by the long history of safe use at monograph doses. These approaches to refine pediatric OTC doses within the framework of the monograph were presented by CHPA at the October 2007, FDA Advisory Committee Meeting on Pediatric Cough and Cold Medicines [1], using pseudoephedrine pediatric pharmacokinetic data. Further details concerning the approaches to pediatric dose determination are reviewed as part of CHPA's response to Question 6 of this submission.

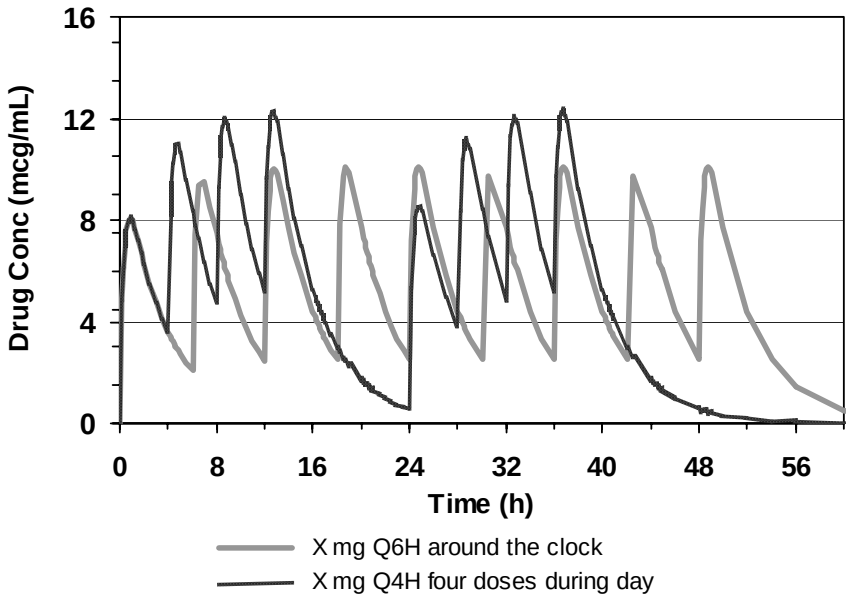
1.4.1.2 Models and Simulations In Support of Future Efficacy Study Designs

There are no plans to conduct multiple-dose pharmacokinetic studies of the cough and cold ingredients in children. Instead, the confirmation or refinement of appropriate pediatric OTC doses can be achieved using pharmacokinetic modeling and simulations of pediatric data from the single-dose studies pooled with historical adult pharmacokinetic data. Furthermore, expected plasma concentrations from different multiple-dose regimens may be simulated, if desired, which would reflect concentrations of drugs attained under actual conditions of home use.

In a study of dosing instructions for a pediatric liquid, 89% of participants noted the correct number of doses and time between doses when asked to indicate the times that they would administer a medicine if they were instructed to dose it three and four times daily [4]. Only 38% correctly indicated this information when they were instructed to administer a medication every 6 hours. Participants commonly misinterpreted this latter instruction as meaning every 6 hours while awake, and to mean only three rather than four total doses.

Plasma drug concentrations for a cough or cold ingredient with a relatively short half-life can be simulated when dosed every 4 to 6 hours to a maximum daily dose (e.g., pseudoephedrine 30 mg every 4 to 6 hours to a maximum of four doses). Figure 1-1 shows two pharmacokinetic multiple-dose profiles simulated with parameters estimated from single-dose data. Compared with dosing at equal 6-hour intervals around the clock, the other 4-hour profile during waking hours may better represent an actual-use pattern or even a dose regimen selected for a future clinical efficacy trial.

Figure 1-1. Simulated Multiple-Dose Pharmacokinetic Profiles of a Short Half-Life Drug When Dosed by Different Regimens



Exploring several dosing strategies in pediatric efficacy studies can be impractical and costly so, where feasible, a pharmacometric approach may be considered. Pharmacometrics is an emerging science designed to inform decisions by conducting quantitative analysis that may include simulation techniques to examine different dosing regimens or future study designs [5]. Depending on the cough or cold ingredient, multiple-dose simulations using single-dose pediatric pharmacokinetic data can be used to design

(or support) future efficacy and pharmacodynamic studies [2]. For example, different dosing patterns can be explored from which optimal times for efficacy assessments over a single day of dosing in a clinic or over a few days in the home setting may be derived.

1.4.1.3 Comments on Dose Ranging and Dose Response

At this time, the CHPA Pediatric Task Force does not plan to conduct pilot efficacy studies for dose ranging prior to large-scale studies. Alternative strategies for dose ranging in children [6], which include pharmacokinetic and allometric scaling models, have been used in drug research to define appropriate pediatric doses. As discussed previously, where current pediatric doses are confirmed or refined using pharmacokinetic data, they will be reaffirmed in future efficacy studies to support the OTC Cough and Cold Monograph.

Doses for new drugs are sometimes based in part on a clinical research program that can distinguish graded responses (efficacy or pharmacodynamics) to different drug exposures (dose, plasma concentrations, or pharmacokinetic parameters). However, this is not feasible in children for all therapeutic classes or individual drugs, especially for those drugs that provide temporary symptom relief, have a shallow dose-response curve in adults, or are assessed using subjective rating scores by children or their proxies.

In a published study of children ages 8 to 15 years with chronic rhinitis, symptomatic groups based on subjective assessments of mild, moderate, or severe did not differ from one another in their response to an objective decongestion test[*] [7]. Significant differences were found only between each group of children with chronic rhinitis (asymptomatic, mild, moderate, or severe) and the healthy control group, indicating the limited sensitivity of graded subjective assessment of nasal stuffiness by children.

Moreover, it is known that demonstrating dose response of oral antihistamines in placebo-controlled clinical trials of allergic rhinitis often fails in adults and has yet to be achieved in the pediatric population [8]. This is true despite the fact that these drugs are evaluated for symptom relief over two to four weeks. The common cold is a self-limiting condition, and symptoms resolve quickly within five to seven days, thus making graded subjective symptom assessments to distinguish a dose response even more difficult. Similarly, no difference in treatment effect could be demonstrated between two doses of oseltamivir taken for five days by adults with influenza [9].

An understanding of dose-response failures in the allergic rhinitis clinical model would be instructive in designing future pediatric efficacy studies. A low therapeutic effect and children being less reliable historians than adults are two potential factors cited as explanations for failed pediatric efficacy trials of loratadine in seasonal allergic rhinitis (SAR) whereby the medical reviewer concluded that, “The choice of the appropriate dose for the

[*] Active anterior rhinomanometry

expected populations (adult and children) will be based on pharmacokinetic assessments …[10]”

Two dose-ranging studies of fexofenadine in children 5 to 12 years compared the 15-, 30-, and 60-mg doses twice daily. One study showed no separation from placebo for any dose and was thought to be due to a high placebo response. The other showed statistically significant improvement for all three doses, but no dose response. The medical reviewer commented [11]: "Nonetheless, difficulty in demonstrating efficacy in the treatment of SAR in the pediatric population is well known and has been seen in other trials of similar design. This difficulty is thought to be due to the use of symptom diaries where the successful demonstration of treatment effects depends on the ability of young children to perform daily evaluations of their symptoms in a thoughtful and consistent manner."

Although corticosteroids are more directly targeted at the underlying cause of allergic rhinitis, which likely increases the efficacy of nasal steroids compared with antihistamines, dose response was not demonstrated in children for the fluticasone propionate [12] and budesonide nasal sprays [13]. In a published review [14] of pediatric antihypertensive studies from 1998 to 2005, three failed and three succeeded to show dose response. Interestingly, the failed studies evaluated a 2- to 9-fold dose range, whereas the successful studies evaluated a 20- to 32-fold dose range.

1.4.2 Instruments and Endpoints

1.4.2.1 Based on Pharmacological Effects and OTC Monograph Indications

Where effectiveness of a cough or cold ingredient will be reaffirmed with placebo-controlled pediatric efficacy trials and/or pharmacodynamic studies (Scheme 2A), the primary endpoints will be based on pharmacological responses. These endpoints, whether objective or subjective, will map directly to the indications permitted by the OTC Cough and Cold Monograph. Table 1-3 provides a selection of labeling text with regard to the indications for use of orally administered cough and cold ingredients under 21 Code of Federal Regulations (CFR) Part 340 Subpart C [15].

1.4.2.2 Comprehensive Review of Subjective and Objective Endpoints

The CHPA Pediatric Task Force has not completed its comprehensive review and assessment of potential instruments and endpoints, so it is too premature to select them. Subjective assessments may be affected by numerous factors that influence the study subject’s experience of symptoms, including expectations, emotions, personality, personal perception, and basis of reference.

Table 1-3. Overview of Labeling Text for OTC Drug Products and Cold Symptoms

Therapeutic Category	Active Ingredients	Indication
Nasal Decongestants	Pseudoephedrine HCl Phenylephrine HCl	Temporarily relieves nasal congestion due to the common cold, hay fever, or other upper respiratory allergies (allergic rhinitis), Temporarily relieves • nasal and sinus congestion • stuffy nose • clogged up nose Reduces swelling of nasal passages, shrinks swollen membranes, helps decongest sinus openings and passages, and promotes nasal and/or sinus drainage.
Antitussives	Dextromethorphan HBr Diphenhydramine HCl	Temporarily (relieves, alleviates, calms, quiets, reduces, or suppresses) cough due to minor throat and bronchial irritation occurring with a cold or inhaled irritant. Temporarily helps • you cough less • to suppress the impulse to cough • reduce the cough reflex that causes coughing • decrease the intensity of coughing
Expectorant	Guaifenesin	Indicated to • help loosen phlegm (mucus) and thin bronchial secretions • rid the bronchial passageways of bothersome mucus • make coughs more productive
Antihistamines	Brompheniramine Maleate Chlorpheniramine Maleate Diphenhydramine HCl Doxylamine Succinate	Temporarily (relieves, alleviates, decreases, or reduces) these cold symptoms: • runny nose • sneezing

Key: HCl – hydrochloride, HBr - hydrobromide

Conceptually, the study subject, where possible, should make all subjective assessments of symptoms rather than the physician or caregiver (e.g., parent or guardian), because the latter may filter information [16]. However, there are additional considerations when evaluating symptoms in pediatric populations with regard to the range of abilities to understand and communicate subjective assessments. The youngest children (ages 2 to under 6 years) would need caregiver reporting of changes in symptom severity or relief, so the use of objective endpoints may be desirable, where they are available.

Nevertheless, some subjective instruments that have been used successfully to measure improvement in nasal symptoms in children with upper respiratory allergies may be adaptable to the acute cold model without further development. Objective instruments and endpoints for nasal and chest congestion symptoms, and for cough, may need to be assessed in exploratory pilot studies to determine their sensitivity and reliability in children. See Scheme 2A on endpoints.

1.4.2.3 Single-Symptom Scores versus Multiple-Symptom Composite Scores

Most adults and children report more than one symptom when suffering from the common cold. They may experience one or more of the following respiratory symptoms: nasal congestion, rhinorrhea, sneezing, cough, postnasal drip, excess airway mucus, chest congestion, or difficulty coughing up phelgm. They may also experience one or more systemic symptoms: fever, sore throat, myalgia, chills, sweats, malaise, fatigue, headache, nausea, or vomiting. Research in naturally acquired and artificially induced colds confirms that symptoms tend to occur in a predictable pattern over 7 to 10 days of a typical uncomplicated viral infection in adults [17,18,19,20]. The mean duration of a simple upper respiratory infection in young children is 7 to 8 days, and percentage lasting for more than 15 days ranges from 6.5% to 13% [21].

Pharmacologic therapy with OTC cough and cold medicines is one option in the management of concurrent symptoms due to the common cold, as they are intended to provide temporary relief of symptoms. Based on the pharmacological actions, each OTC ingredient relieves at least one, but not most, cold signs or symptoms.

Under the monograph system, the OTC cough and cold ingredients are indicated to temporarily relieve or reduce the following signs or symptoms due to the common cold or other respiratory conditions:

- nasal congestion – phenylephrine and pseudoephedrine
- rhinorrhea and sneezing – brompheniramine, chlorpheniramine, diphenhydramine, doxylamine
- cough – dextromethorphan, diphenhydramine
- chest congestion and thick airway mucous - guaifenesin

The design of future pediatric efficacy studies of a single ingredient should consider whether the child's experience of multiple cold symptoms might unduly influence the subjective rating score for the relief of a single cold symptom. Subjective symptom assessments in these efficacy studies would not be strictly independent variables. For example, nasal secretions (rhinorrhea) may affect the symptom rating score for congestion (blockage), because rhinorrhea and congestion are predominantly determined by sensory neural stimulation [16].

Another consideration is the "halo" effect that several cold symptoms may have, if untreated, on a subjective global assessment of a single-ingredient cold medicine. Although the child's nasal congestion may improve with treatment with pseudoephedrine in a study, for example, he or she may be experiencing untreated headache, nausea, fever, sneezing, and fatigue at the same time. Scoring of the global assessment of pseudoephedrine by a caregiver or older child in this situation may reflect the lack of a pharmacological effect or improvement in the other signs and symptoms.

A similar situation exists for antihistamines that are prescribed to alleviate multiple allergy symptoms. Primary efficacy endpoints using composite rating scores of several symptoms associated with allergic rhinitis have been evaluated in both successful and failed placebo-controlled, pediatric studies of antihistamines. In FDA's review of the pediatric trials of loratadine syrup [10], the medical officer wrote, "Using a single symptom assessment as the primary efficacy parameter is a more stringent requirement for establishing efficacy than that based on composite scores, and is not how our Division generally evaluates allergic rhinitis drugs." Instead, FDA recommends in its draft guidance that the primary efficacy endpoint be a composite symptom score, such as the total nasal symptom score (TNSS), which includes the symptoms of rhinorrhea, nasal itching, nasal congestion, and sneezing [22].

These insights are important to consider when designing an efficacy study of a single monograph ingredient that will alleviate only one cough or cold symptom. For example, to reaffirm the effectiveness of pseudoephedrine alone for nasal congestion or dextromethorphan alone for cough in the acute cold model using subjective symptom

scoring, the study population may need to be enriched with children having the particular cold symptom with at least moderate severity. Alternatively, if individual ingredients have been shown to be effective separately in adults, it may be reasonable to reaffirm the effectiveness of individual ingredients as part of a combination in children, especially where the cold symptoms are commonly concurrent and each ingredient relieves different symptoms. This can be accomplished with composite and single symptom scores as endpoints.

1.4.3 Challenges and Opportunities with Acute Cold Studies

1.4.3.1 Well-Designed Clinical Trials

A well-designed and well-conducted clinical trial is critically important to demonstrate the safety and efficacy of therapeutic agents intended to *treat signs and symptoms* of a disease or pathological condition, such as those associated with the common cold, allergic rhinitis, and sinusitis. FDA has provided the pharmaceutical industry with draft guidances on clinical development programs for allergic rhinitis drugs [22] and non-antimicrobial sinusitis drugs [23]. There is no FDA guidance available for drugs that treat symptoms of the common cold, although some key design elements from allergic rhinitis and sinusitis studies in the treatment of symptoms could apply.

It is known that allergic rhinitis and cough-cold drugs may occasionally fail to show effectiveness in otherwise well-conducted adult studies [22,24]. This is due in part to the subjective nature of symptom assessments and intersubject variability of the symptom complex. To increase the likelihood of a successful study, the number of efficacy variables should be kept at a minimum, and they should be related to the drug's expected pharmacological action [16].

Natural acute cold studies in adults may not demonstrate drug efficacy in all instances because of the diminishing signal from resolving illness reduces apparent effect size [24]. In colds due to rhinovirus, which accounts for an estimated 40% to 50% of natural colds in adults, symptoms peak on the second day after exposure and decline over three to four days. Therefore, when conducting clinical studies in adults or children with colds, it is important to ensure that subjects are enrolled as soon as possible after the onset of illness when treatments are expected to have their greatest benefit. In some published adult and pediatric studies examining the efficacy of treatments for cold symptoms, subjects are already entering the recovery phase of the cold at the beginning of the study [24]. For this reason, multiple-day studies may be confounded by natural progress of the condition.

1.4.3.2 Underlying Variability of Nasal Symptoms and the Placebo Effect

Although the general population commonly experiences nasal congestion, it is a symptom that is not always easily described by a patient and interpreted by a clinician [25]. Patients and clinicians are interested in those aspects that cause discomfort and these symptoms may not always correlate with measures of nasal patency. Nasal congestion is described subjectively according to how it is perceived by an individual person. Factors that influence the perception of nasal congestion are nasal resistance to airflow; stimulation of cold receptors in the airway; congestion of the ethmoid area, paranasal sinuses, and Eustachian tube; and mood [25]. Synonymous terms include nasal stuffiness and nasal obstruction, which reflect swollen nasal passages and membranes and the feelings of sinus pressure.

The Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology has questioned the reliability of subjective perception of nasal stuffiness [26], and has, as recently as 2003, affirmed that precise criteria for the objective assessment of nasal obstruction have yet to be determined [27]. Regarding the clinical evaluation of nasal symptom severity, these guidelines suggest the use of a seven-point visual analog scale. By contrast, FDA's draft guidance cites a nasal symptom rating system commonly used in allergic rhinitis trials that follows a four-point (0 to 3) scale. These and similar issues will need to be sorted out in the design phase of the pediatric efficacy trials.

1.4.3.3 Underlying Variability of Cough and the Placebo Effect

There are factors related to the nature of cough itself that make it challenging to demonstrate the efficacy of cough medicines in clinical studies in children and adults. The impact of such factors on clinical trial design, especially with regard to endpoint selection and sensitivity, needs consideration. For example, the study of cough in children is complicated due to the finding that there is a wide range of cough frequency from 1 to 34 times a day in normal children [28]. Also, there is spontaneous resolution of cough during the course of a study [29]. Because nonspecific acute cough resolves naturally in 50% of young children within one week [30], 85 children per study arm would be required in a randomized controlled trial to detect a 50% difference between active and placebo groups, for a study powered at 90% at the 5% significance level.

Another important factor is that cough is subjected to psychological influences [31]. Adult studies have shown that administration of placebo is associated with a large antitussive effect, resulting in a 40% to 50% reduction in cough frequency. In a comparison of no treatment and placebo treatment in adults who had a dry or slightly productive cough associated with an upper respiratory tract infection, Lee *et al* [32] found that placebo treatment was associated with not only a significant decrease in cough frequency but also an increase in cough suppression time. This research group suggested that the antitussive effect associated with placebo may not be solely explained by a voluntary effort to reduce

cough, but may be related to the generation of central neurotransmitter such as endogenous opioids.

In 2006, the American College of Chest Physicians (ACCP) published a document addressing the assessment of cough severity and efficacy of therapy in clinical research [33]. While this document does not specifically address pediatrics and concentrates mainly on chronic cough, it does provide some insights that may facilitate the design of studies in children with acute coughs due to colds. In general, the guidelines suggest that investigators should use both objective and subjective methods to assess cough because they have the potential to measure different aspects.

1.4.3.4 Evaluation of Airway Mucus or Sputum

Limited published information is available on the evaluation of drugs that act on the airway secretory system to increase the expectoration of mucus or sputum. In efficacy trials, adults have provided subjective impressions of sputum changes during drug treatment compared with placebo. For example, sputum has been rated using verbal category descriptive (VCD) scores [34] for

- volume - none, less than initial, same as initial, and more than initial;
- thickness - thin, thick, and solid;
- ease of rising – normal ease, difficult, and very difficult.

Sputum quantity and thickness have been scored for severity based on a 12-point scale, with 12 being most severe. In addition, a visual analog scale (0–100 mm) for ease of expectoration with ends of the scale being ‘very difficult to expectorate’ and ‘extremely easy to expectorate’ has been used.

Subjective assessments of airway mucus or sputum are expected to be highly variable and inconsistent in children, especially in young children for whom parents or guardians would score changes based on their impressions. Therefore, it would be reasonable to consider a double-blind, placebo-controlled pharmacodynamic study with objective measurements. Changes in sputum volume and selected biochemical and rheologic properties of sputum as predictors of clinical outcome should be considered to reaffirm effectiveness of guaifenesin in children with chest congestion. Still, the effects of drugs that act on the airway secretory system are difficult to assess [35], because the measurement of sputum volume is not easy and there is no absolute way of measuring the quantity of airway secretions in humans.

Changes in biomarkers of mucus secretion and plasma exudation in sputum should be considered [36]. Samples of sputum may be analyzed for changes in these biomarkers using procedures and methods that have been reported in clinical drug trials that examined sputum production in chronic bronchopulmonary disease [37], chronic bronchitis [35], and

asthma [38]. However, the use of these biomarkers as objective endpoints may need further development with regard to their application to acute colds, chest congestion, or other respiratory conditions, such as bronchitis, in children.

The mucociliary system of the airway protects the lungs, and requires an adequate quantity of mucus with appropriate rheological quality and adequately functioning cilia. The "hydration hypothesis" proposes that guaifenesin, by increasing the effective hydration of the respiratory tract, maintains the sol layer needed for ciliary clearance and reduces the viscosity of respiratory mucus, thereby further facilitating its removal by natural clearance processes [39]. Data suggest that mucociliary clearance occurs in the trachea and main bronchi at a similar rate as in the nose [40]. Therefore, another plausible objective measure of guaifenesin effectiveness that could be explored in children may be nasal clearance time (NCT) using the saccharin method [41,42]. If shown to be feasible and sensitive in measuring drug effects in children, a decrease in NCT could be a surrogate marker for the thinning of mucus in the bronchi.

Although NCT has not been used in an efficacy trial of guaifenesin in the common cold, changes in NCT were measured after daily oral treatment with chlorpheniramine or placebo in adults with viral-induced colds [43]. In this study, significant decreases in NCT for chlorpheniramine when compared with placebo may be due to a decrease in nasal secretions that may help improve mucociliary clearance.

1.4.4 Challenges and Opportunities with Pediatric Research

While there have been significant advancements in pediatric research over the past 10 to 15 years, the industry-sponsored, pediatric research program of OTC cough and cold ingredients will consider challenges and opportunities associated with pediatric research in the design of new efficacy and/or pharmacodynamic studies. Highlights of some published research studies on the assessment of symptoms in children follows.

1.4.4.1 Research on Assessment of Nasal Congestion in Children

Clinical investigators have published studies on the sensitivity and reliability of subjective and objective methods used in children to assess nasal congestion. In a study of children ages 8 to 15 years with chronic rhinitis, symptomatic groups based on subjective assessments of mild, moderate, or severe did not differ from one another in their response to the objective decongestion test[†] [7]. Significant differences were found only between each group of children with chronic rhinitis (asymptomatic, mild, moderate, or severe) and

[†] Active anterior rhinomanometry with mask was performed via a computerized rhinomanometric system

the healthy control group, indicating the limited sensitivity of graded subjective assessment of nasal stuffiness by children.

In another study of potential correlations between subjective (nasal stuffiness) and objective (anterior rhinometry) measures, the investigators noted that children ages 8 to 15 years have difficulty in self-assessment of nasal symptoms and are poor judges of the presence or severity of nasal obstruction [44]. These investigators also suggested that higher scoring variability might be due to parents who assist children in filling out home diaries.

By contrast, other clinical researchers demonstrated a statistically significant, although weak, correlation between the subjective and objective assessments of nasal congestion after histamine provocation [45]. In this study of the localized physiologic response of the nasal mucosa to histamine provocation, nasal congestion was measured subjectively and objectively before, and five minutes after, applying a 0.4-mL histamine nasal spray to each nostril. Ninety-eight healthy children (7 to 17 years) and 102 healthy adults (18 to 53 years) were asked to grade their nasal congestion (stuffiness) as 1 – none, 2 – slight, 3 – moderate, and 4 – severe in each nasal cavity. Nasal congestion was evaluated objectively using acoustic rhinometry to measure the minimal nasal cross-sectional area (MCA). The study results demonstrated similar increases in mean subjective nasal congestion scores after histamine provocation: 1.6 ± 0.4 to 2.0 ± 0.5 ($p < 0.0001$) in children and 1.7 ± 0.4 to 2.1 ± 0.5 ($p < 0.0001$) in adults. Mean MCA (cm^2) also decreased significantly within each group, indicating increased nasal obstruction: 0.52 ± 0.14 to 0.37 ± 0.10 ($p < 0.0001$) in children and 0.58 ± 0.18 to 0.46 ± 0.15 ($p < 0.0001$) in adults.

1.4.4.2 Research on Assessment of Cough in Children

Cough frequency may be measured objectively using cough meters, and these devices show promise as a tool for evaluating cough treatments in children. Yet, successful use of these devices would require continuous monitoring [46], because attached microphones can become dislodged and some children may not tolerate wearing them due to itching at the site of electrodes [31,46]. While some pediatric clinical studies use subjective change in nocturnal cough to assess treatment efficacy, this parameter has been unreliably reported [46,47].

Multiple subjective assessment tools have been used to monitor cough, including verbal category descriptive scores and visual analogue scores that may be completed by both children and parents. Chang and colleagues have conducted several studies examining the assessment of cough. In one of these studies, the group demonstrated a poor correlation between objective measurement of cough using a cough meter and the subjective assessment of the presence of nocturnal cough by both children and parents [46]. There was a better correlation between objective measurement of cough and subjective assessment of daytime cough. This group also demonstrated that there are

differences in how well verbal category descriptive (VCD) scores and visual analogue (VAS) scores completed by children and parents correlate with objective measurement of cough. The VAS was vertically marked from 1 to 10, with 10 representing the most severe cough and 1 the absence of cough. The verbal category descriptive score completed by children 6 to 17 years with cough correlated better with an objective measurement of cough than the VAS completed by the same children. In addition, there was a better correlation with objective measurement of cough when the VCD score was completed by the children rather than by their parents [46]. The VCD scoring for daytime cough:

0 = no cough;

1 = cough for one or two short periods only;

2 = cough for more than two short periods;

3 = frequent coughing but does not interfere with school or other activities;

4 = frequent coughing which interferes with school or other activities;

5 = cannot perform most usual activities due to severe coughing.

1.4.4.3 Research on Assessment of Airway Mucus in Children

Data suggest that mucociliary clearance occurs in the trachea and main bronchi at a similar rate as that in the nose [40]. Therefore, research on nasal mucociliary clearance in healthy children and in children with various respiratory conditions may be applicable to the design of future pediatric clinical studies for antihistamines and expectorants with regard to pharmacological effects on nasal secretions and bronchi mucus, respectively.

The saccharin test has been used to study the nasal mucociliary clearance in children. In a study of 295 randomly selected school children, NCT was measured and analyzed according to clinical history (bronchial asthma, rhinitis, asthma with rhinitis, and acute upper respiratory tract infections) [42]. In a subset of 50 children, the saccharin test was repeated in the same nostril the following day to assess its reproducibility. The results confirm that the saccharin test is an useful screening technique for measuring nasal mucociliary clearance in children, because it is inexpensive, simple to do, and reproducible [42]. Additional research is needed to distinguish differences in NCTs among children with respiratory conditions, although NCTs were longer than those in healthy children.

In a more recent study, the nasal mucociliary clearance was measured using a saccharin test in 100 healthy children, ages 4 to 15 years, from a tropical region [48]. Clinical investigators found that NCT was 5.7 $\pm$ 2.59 minutes in males and 6.4 $\pm$ 2.59 minutes in females with no significant difference between groups. Whether the saccharin test can distinguish differences in treatment effects between active and placebo groups in children with colds or other respiratory conditions would need to be evaluated.

1.4.4.4 Special Considerations for Younger Children

Schemes 2A and 2B outline general approaches to reaffirm effectiveness of the cough and cold ingredients in children. Although it is too premature to choose an approach for each ingredient, the availability of reliable instruments and endpoints for younger and older children and whether they are the same for both age groups, may necessitate different research pathways. The CHPA Pediatric Task Force would consider the advantages and disadvantages, and scientific merit, of different possibilities:

- enroll children of all ages in the same efficacy or pharmacodynamic study
- initiate an efficacy study in older children and follow with a bridging pharmacodynamic study in younger children with an acceptable objective endpoint
- conduct an efficacy study in older children and bridge to younger children with pharmacokinetic exposure data, where appropriate

1.5 Adjacent and Overlapping Research Questions

1.5.1 Adolescents

The pharmacological responses of cough and cold OTC ingredients are unlikely to be different between adolescents and adults, which contrasts to those drugs whose pharmacological responses are dependent on maturation of receptors with chronological age or sexual maturity. Thus, it is reasonable to expect that similar systemic exposures, and by corollary, similar doses will be necessary in adolescents and adults to provide similar relief of signs and symptoms. Moreover, metabolic pathways for cough and cold ingredients are fully mature before adolescence. Thus, body composition differences are unlikely to produce large enough pharmacokinetic differences that would warrant dose adjustment versus current paradigm.

Adolescents from 12 to under 18 years of age are included in most of the new pediatric pharmacokinetic studies as part of the industry-sponsored, pediatric research program. These studies will provide valuable additional data that can be useful in the modeling and simulation of drug exposures in this ages group. Where adolescent pharmacokinetic data indicate comparable exposure to that in adults at the same doses, then the current OTC indication for the cough and cold ingredient would be supported by available adult effectiveness data. Therefore, additional efficacy studies in this cohort are not necessary. Further details concerning adolescents are provided as part of CHPA's response to Question 5 in this submission.

1.5.2 Combination Products

As a general principle according to FDA's OTC combination policy, when effectiveness data are available for individual ingredients, additional study of the combination of ingredients is not needed to confirm efficacy when there is clear differentiation of pharmacological actions. Therefore, where new effectiveness data are generated for single ingredients in children, then pediatric efficacy studies for combination products comprised of these ingredients are not necessary. Alternatively, if individual ingredients have been shown to be effective separately in adults, it may be reasonable to reaffirm the effectiveness of individual ingredients as part of a combination in children, especially where the cold symptoms are commonly concurrent and each ingredient relieves different symptoms. This can be accomplished with composite and single symptom scores as endpoints. See discussion on advantages of composite endpoints in Section 1.4.2.3.

If the potential for a drug-drug interaction among combined ingredients is scientifically plausible based on metabolic pathways, then available data on such interactions would be reviewed, or generated if necessary, using *in vitro* methods and/or adult pharmacokinetic studies as outlined by FDA's guidance [49]. If any drug-drug interactions are found in adults and would be clinically relevant to adjust OTC doses, then additional studies in children may be warranted to confirm these interactions. Research in children should be performed only when necessary to answer new and relevant scientific questions. Further details concerning combination products are reviewed as part of CHPA's response to Question 8 in this submission.

1.6 Input from FDA and External Experts

The clinical evaluation of the ingredients used to treat the signs and symptoms associated with common colds in pediatric populations presents challenges and opportunities for a pediatric research program, as outlined in the previous sections. In order to conduct the research program effectively, the CHPA Pediatric Task Force will require consultation and input from both FDA and external experts to augment scientific support. Identification of optimal methods to reaffirm efficacy in the pediatric populations for each ingredient, where needed, will be critical. In instances where adequate methodology is lacking, development of new methods will be necessary.

A multidisciplinary group of experts will play a key role in providing advice on potential methods, instruments, and endpoints, their development if needed, and on overall study designs. Workshops are being considered among industry clinical researchers, invited expert consultants, and FDA representatives to share information and experiences. The CHPA Pediatric Task Force will also seek guidance from FDA on study protocols that will

comprise the research program. Input from FDA is critical to ensure that the studies meet the current standards of pediatric research and are designed sufficiently to reaffirm the efficacy and further support the safety of monograph cough and cold ingredients. The CHPA Pediatric Task Force is committed to advancing the science of these medicines in children through a well thought-out research program.

1.7 Summary

Although there are significant data to show the effectiveness in adults, the body of evidence is not as robust in children in favor of cough and cold medicines. While practical experience for many years by both doctors and parents using these medicines demonstrates that these ingredients are effective in relieving cough and cold symptoms in children, the CHPA Pediatric Task Force intends to reaffirm the science supporting eight monograph ingredients. To determine appropriate dosing, reaffirm effectiveness, and further support the safety of cough and cold ingredients in children, ages 2 to under 12 years, the pediatric research program sponsored by industry should integrate and bridge historical data with new data obtained across study types and populations.

Given the scope and anticipated complexity of an industry-sponsored pediatric research program, the CHPA Pediatric Task Force has assembled the decision points, historical data sources, and potential new studies into a high-level, generic road map consisting of three schemes. This road map is a starting point based on current thinking, and does not represent industry commitments for specific types and number of studies for each ingredient. It is intended to facilitate ongoing discussions among companies of the CHPA Pediatric Task Force, divisions of FDA, and academic research experts.

1.8 Reference List for Question 1

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Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 2

FDA Question:

"Should cough and cold products for the pediatric population continue to be available OTC, or should they be made available only by prescription?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 2

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2 FDA QUESTION 2

"Should cough and cold products for the pediatric population continue to be available OTC, or should they be made available only by prescription?"

2.1 Cough And Cold Products Should Continue To Be Available OTC

Pediatric cough and cold products should be labeled for OTC use for all ages. Analysis of data from years of real-world use demonstrates that serious adverse events are very rare and parents can and do properly recognize and treat their children's colds. Pediatric cough and cold products are appropriate for self-medication and do not meet the criteria to be made available only by prescription.

- Data submitted through the OTC Review and through the deliberations of a joint meeting of the Nonprescription Drugs Advisory Committee (NDAC) and the Pediatric Advisory Committee in October 2007 demonstrate that pediatric cough and cold medicines do not meet FDA's definition of prescription drugs, as drugs are classified as prescription based on their toxicity, potentially harmful effects, methods of use, or the collateral measures required for its use.[1] The reverse switch of pediatric cough and cold products from nonprescription to prescription status is not a practical or efficient way to actually address whether the products have been shown to be safe and effective for pediatric use.

- If these medications were reverse switched to prescription status, there would be a negative socioeconomic and public health impact.

- A change to prescription status would present difficult legal and regulatory problems, including the need for an amendment to the relevant final OTC drug monograph and the approval of NDAs for the affected products.

- The ultimate resolution for the question raised by FDA from a legal and regulatory perspective should consist of a combination of revised OTC labeling directed to consumers and labeling for healthcare professionals, as has been done for other OTC drugs.

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[1] Collateral measures are defined as: Acceptable safety profile; Low misuse and abuse potential; Reasonable therapeutic index of safety; Use non-Rx is safe and effective; Condition can be self-recognized, self-treated; Health practitioner not needed

2.2 These Medicines Do Not Meet Exemption Requirements of the Law that Would Require a Prescription

The medicines with these ingredients do not meet exemption requirements of the law that would require that they be dispensed only on prescription: Data submitted through the OTC Review and through the deliberations of NDAC in October 2007 demonstrate that pediatric cough and cold medicines do not meet FDA's definition of prescription drugs. The method to use medicines with these ingredients can be readily labeled, particularly given parents can readily recognize the signs and symptoms they are intended to treat, and there are no collateral measures necessary for use, such that they are not safe for use except under the supervision of a physician or other prescriber.[2]

2.3 An Attempt to Change the Status of These Products to Prescription Status Would Present Difficult Legal and Regulatory Issues

Under the cold, cough, allergy, bronchodilator, and antiasthmatic monograph, the eight ingredients discussed through this submission, when marketed in accordance with the relevant monograph provisions, are generally recognized as safe and effective (GRAS/E).[3] This is to say they are not "new drugs." The ingredients under monograph conditions are not subject to NDAs. They have been used for a material time and for a material extent, and a panel of experts with appropriate scientific training and experience assessed these ingredients through the OTC Review process.

As a threshold matter, to change the status of these ingredients to prescription status would require an amendment to the relevant monograph, which, absent special circumstances not under consideration in this instance, would require notice and rulemaking.[4] But removing these ingredients from the monograph for pediatric populations through a monograph

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[2] See Federal Food, Drug, and Cosmetic Act sec. 503(b)(1) [21 USC 353(b)(1)] providing "A drug intended for use by man which –

(A) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

(B) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug;

Shall be dispensed only

(i) upon a written prescription of a practitioner licensed by law to administer such drug . . . ."

[3] 21 CFR Part 341.

[4] See 21 CFR 330.10(a)(14), describing the procedure for monograph amendments.

amendment would not in itself convert them to prescription drugs. Rather, they would be unapproved new drugs.

FDA policies make it clear that drugs lacking the requisite approval, including those that are not marketed in accordance with an OTC drug monograph, are not seen as having evidence demonstrating that they are safe and effective. The agency has therefore stated that such products are new drugs that must be approved by FDA to be legally marketed.[5] While FDA has outlined its enforcement priorities on when it will act against such drugs, there is no FDA recognized category of "not new" drugs outside of the OTC Review monograph process. If FDA were to seek to do otherwise, it could be deemed inconsistent with the ruling in *Cutler v. Kennedy*, 465 F. Supp. 838(D.D.C. 1979), which held that the agency cannot "affirmatively sanction" the marketing of new drugs without approved NDAs.

Assuming the agency nonetheless amended the monograph to remove pediatric indications and requested that manufacturers submit new drug applications, there would still be further complications. It is possible that such an application could be submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), which the Agency interprets to permit applications based on a "finding" of safety and effectiveness, including a finding made in the OTC Review. Such applications might not be required to contain the safety and effectiveness data ordinarily required in an NDA submitted under section 505(b)(1).

In this circumstance, however, the NDAs would need to contain full information on chemistry, manufacturing, and controls, in the same detail as required for any new drug. In addition to requiring review by FDA, preapproval inspections of facilities described in the NDAs, both domestic and foreign, would need to be conducted.

Today, there are hundreds of medicines with these ingredients in the OTC marketplace (and thousands if each store brand and all sizes are counted separately). Today, dosage forms of these medicines change frequently to respond to consumer needs. In light of this, FDA would need to anticipate a high volume of applications, imposing a substantial burden on industry and the agency, including reviewers and field personnel. User fees would not be available to defray the cost of such a new burden, since such fees are not charged for section 502(b)(2) applications.

This diversion of limited resources is unnecessary since the OTC Review was created for the very purpose of meeting resource challenges of many applications for different OTC medicines with the same ingredients for the same indications. At the start of the OTC

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[5] See Compliance Policy Guide on marketed new drugs without approved NDAs or ANDAs, CPG 7132c.02.

Review, FDA noted it was taking the category rather than a product-by-product approach since "the limited resources of the Food and Drug Administration would be overwhelmed by attempting to review separately the labeling and the data on the safety and effectiveness for each OTC drug now on the market."[6] The agency summarized the benefits of a category rather than a drug-by-drug approach as addressing a lack of funds, a lack of personnel, and competitive unfairness if a drug-by-drug approach was adopted.[7] "A drug-by-drug approach is not the best method of proceeding, since it would be so cumbersome, time consuming, and confusing."[8]

2.4 Prescription Status Would Come at a Cost

If FDA were to unnecessarily move forward and overcome the procedural challenges involved in making pediatric indications available only by prescription, it would have a negative impact on society through the loss of the cost-savings and cost-benefits of OTC medicines.

Absenteeism from school due to the common cold already causes an estimated 189 million school days lost annually and increased healthcare professional interaction.[9] Reducing availability of cough and cold medicines to treat the symptoms of colds would only drive this loss higher.

For society in general (adults and children), Lipsky estimated self-treatment of cough and cold symptoms saves the United States $4.75 billion a year through improving work productivity, reducing unnecessary doctor visits, and taking prescription medicines only when appropriate.[10] Unneeded removal of OTC cough and cold medicines for a significant percentage of the population – children 4 through 11 – would reduce these savings without providing a measurable gain.

The unnecessary costs of a move to prescription status would come against a context of very rare serious events and, as discussed in the response to Question 3, in a category where parents have a long history of using these medicines.

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[6] See 37 Fed. Reg. 85, 86 (January 5, 1972).

[7] 37 Fed. Reg. 9464, 9465 (May 11, 1972).

[8] Id.

[9] Fendrick, 2003.

[10] M. Lipksy, et al., "An Economic Analysis for Treating Viral Upper Respiratory Tract Infection in the United States," presentation to the World Self-Medication Industry Asia/Pacific regional conference, October 28, 2004 (and Northwestern University press release, October 26, 2004).

2.5 The OTC Review Process is Better Suited to Address the Issues Raised

FDA need not follow the path of changing the status of monograph oral cough and cold ingredients to prescription status for pediatric populations to address the questions pending before the agency. A change in status of these ingredients from nonprescription to prescription status is neither a practical nor efficient way to deal with the core issues before the agency, which are instead best dealt with as described in the responses to Questions 1, 6, and others in this submission.

The questions the agency raises, including the question of their continued OTC availability, are best dealt with through FDA's OTC Review monograph system, under which the agency can review data from industry and other interested parties. Because the ingredients under consideration have long been used by many manufacturers, OTC Review procedures, rather than individual NDAs, are well suited to developing an industry-wide answer in an open, transparent manner. In contrast, the primary means used to evaluate prescription drugs, the NDA process, would close off the possibility of an industry-wide, open process. Similarly, the NDA process would close off the possibility of input from other interested groups.

In addition, utilizing the prescription pathway would create unnecessary administrative effort and expense, potentially take years to complete, and would not address the actual issues that FDA is seeking to address: gathering additional information to confirm the effectiveness and safety of OTC medicines with these ingredients for children. Prescription status also does not address the predominant root cause of the serious adverse events--accidental ingestions and misdosing or misuse which can still happen with prescription products. Instead, FDA should use the process already established to address precisely these questions: the OTC Review.

2.6 Summary

Pediatric cough and cold products are appropriate for self-medication and do not meet the criteria to be made available only by prescription. A change to prescription status would present difficult legal and regulatory problems, including the need for an amendment to the relevant final OTC drug monograph and the approval of NDAs for the affected products. The ultimate resolution for the question raised by FDA from a legal and regulatory perspective should consist of a combination of revised OTC labeling directed to consumers and labeling for healthcare professionals, as has been done for other OTC drugs.

Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 3

FDA Question:

"If the pediatric indications and dosing for cough and cold products were no longer available OTC, would the public use the adult formulations of the OTC monograph products for children, and thus create a greater risk of misuse or overdose?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 3

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3 FDA QUESTION 3

"If the pediatric indications and dosing for cough and cold products were no longer available OTC, would the public use the adult formulations of the OTC monograph products for children, and thus create a greater risk of misuse or overdose?"

3.1 To Minimize Risks from the Inappropriate Use of Adult medicines for Children, Education and Labeling Against Use in Children Under 4 are the Most Appropriate Actions

Without OTC pediatric cough and cold medicines, there is a risk that parents could administer either adult formulations of OTC monograph cough and cold products or other alternatives, the safety and efficacy profiles of which are less well studied and less well documented than those of pediatric OTC cough and cold medicines.

To minimize these risks, CHPA has started a multiyear education campaign aimed at encouraging the appropriate use of these medicines in accordance with voluntary label changes by manufacturers transitioning to labeling "Do Not Use" for children under 4 years of age.

3.2 Position of the CHPA Pediatric Task Force

The CHPA Pediatric Task Force position in response to Question 3 is supported by the following:

- When used appropriately at recommended doses, OTC pediatric cough and cold medicines have a safety and efficacy profile that is appropriate for OTC use.
- Multiple data sources demonstrate that administration of adult products to children is a potential risk, especially if the availability of pediatric OTC cough and cold medicines would be further limited.
- Parents and other caregivers want access to OTC cough and cold products for their children, and healthcare practitioners continue to recommend these medicines. To minimize risks, labeling changes instructing parents not to use these medicines in children under 4 years are appropriate

3.3 Parents Want and Need Appropriate Pediatric Products

The common cold is recognized as the most common infectious syndrome of humans [1, 2] with adults experiencing two to four symptomatic infections each year and children experiencing six to eight [3]. Symptomatic treatment of the common cold in adults and children has long been established as acceptable medical practice [4]. With no effective

preventive measure or treatment available for the underlying viruses, medical intervention is limited to symptom relief, facilitating the return to normal function while the condition resolves naturally. For the vast majority of uncomplicated cold episodes in adults and children, management of symptoms with OTC cough and cold medicines (antitussives, nasal decongestants, antihistamines, and expectorants) helps to achieve this objective. Parents want safe and effective options to treat cough and cold in children. It is extremely difficult for parents to watch their child suffer from symptoms that they as adults have effectively treated in themselves with OTC products.

The demand for treatments of cold symptoms is illustrated by survey results finding 73% of parents and caregivers reporting administering an OTC cough medicine to a child in their home who was experiencing a cough [5]. In turn, 56% of parents reported that a child under 18 in their home experienced a cough during the past 3 months [5]. The percentage of parents reporting administering an OTC medicine to a child for nasal congestion was similar: 70% reported using an OTC decongestant with their children with that symptom [6]. Finally, the desire for treatment of common cold symptoms in children is also seen in the Slone Epidemiology Center survey, finding that, in a given week, a cough and cold medication was used by 10.1% of U.S. children [7].

3.4 Surveys Indicate Misuse of Adult Products is a Potential Risk

When asked a hypothetical question about what they would do if cough and cold medicines for children were taken away or relabeled to say there is no evidence that they work, surveys conducted in 2007 and 2008 indicated parents and caregivers could take actions that may result in increased risk. As discussed further in 3.4, by focusing on: (a) children under the age of 4 years, who are at the greatest risk of accidental ingestions and medication errors leading to potential overdose; (b) educational messages aimed at label changes; and (c) including directions not to use these medicines in children under 4, we believe we can mitigate these risks while meeting parents' desire to treat their children 4 and over.

3.4.1 NPR / Kaiser Family Foundation / Harvard School of Public Health (December 2007)

In November 2007, one month after the widely publicized recommendation of the FDA advisory committee in October 2007 that children under the age of 6 years should not be given OTC cough and cold medicines, NPR, Kaiser Family Foundation, and the Harvard School of Public Health conducted a survey in 572 parents of children in this age group [8]. Eighty-six percent of parents said they had heard about the safety and effectiveness discussion. When asked about a hypothetical situation in which FDA would put a label on children's cough and cold medicines saying they have been found to be safe but there is no

evidence that they actually work, 28% said they would still use them without a doctor's recommendation.

3.4.2 Gallup (August 2008)

The 2008 Gallup Study of Concerns for Children's OTC Cold Medications conducted by Multi-sponsor Surveys, Inc., Princeton, NJ, asked a national sample of 759 caregivers of children 6 months to 11 years what they would do if OTC cough and cold remedies were not available [9]. In response to this question, 40% of caregivers said they would use "natural, non-medication" remedies, and 24% said they would use OTC cough and cold medications formulated for older children and adults. These data directly address FDA's Question 3.

3.4.3 Observations

Taken together, the NPR/Kaiser Family Foundation and Gallup surveys suggest that there is a risk that parents might turn to adult medicines if pediatric medicines were no longer available. Further, they suggest parents could turn to other alternatives such as herbal products, dietary supplements, devices, or home remedies, the safety and efficacy profiles of which are less well studied and less well documented than those for OTC pediatric cough and cold medicines. There are undetermined risks in this instance, and many of these products have not been evaluated in children.

Driving parents toward asking doctors for antibiotics raises another potential risk through a potential increase in inappropriate and unnecessary use of antibiotics. This would add costs to the healthcare system from additional doctor visits [10, 11].

Some of the risk involved in the potential use of adult medicines or other less-studied alternatives can be mitigated by addressing parent behaviors that may lead to adverse events among the youngest children through labeling and education, rather than removing pediatric indications for these medicines altogether.

3.5 To Minimize Risks, Labeling Changes Instructing Parents Not to Use These Medicines in Children Under 4 Years are Appropriate

Research shows that dosing errors and accidental ingestions are the leading causes of rare adverse events in young children. As a result, CHPA member companies who are the leading manufacturers of oral OTC pediatric cough and cold medicines are continuing initiatives aimed at encouraging the appropriate use of these medicines, including directing parents and caregivers not to use these medicines in children under 4 years of age.

Selecting a direction against use in children under 4 as an appropriate age is supported by data reviewed by FDA since the October 2007 advisory committee meeting in a published

report from the Centers for Disease Control and Prevention (CDC) about adverse events in children who had ingested cough and cold medications [12]. First, 2- and 3-year-olds are at the greatest risk of accidental, unsupervised ingestions. Second, in the August 25, 2008 *Federal Register* notice that is the subject of this submission, FDA commented that "FDA reviewed the CDC study and underlying data, particularly looking at the type of events that occurred with the reportedly labeled dose of OTC cough and cold medications, and noted that children under 4 years of age are more likely to experience non-allergic adverse events than older children."

The underlying data cited by FDA in the *Federal Register* notice were posted to the docket [12] and have been reviewed by the manufacturers of OTC cough and cold medicines. The data set identifies 77 cases for emergency department visits attributed to cough and cold products without evidence of unsupervised ingestion or administration error in children less than 12 years of age. Seriousness is not reported in the data in FDA's docket, but there were only two reports of hospital admission. In one of these cases, phencyclidine was identified in a toxicology screen. In the other case, a 6-year-old receiving chemotherapy presented with fever and cold symptoms treated with chlorpheniramine and phenylpropanolamine. In all but four cases, the patients were treated and released from the emergency room; two patients were admitted, and two patients left against medical advice. Forty-seven reports were related to an allergic reaction. Thirty reports of non-allergic adverse events are summarized below (note: in contrast to "adverse drug reaction," "adverse event" does not imply causality):

- Events reported in 21 cases of children less than 4 years of age (0, 1, 2, and 3 years) were mainly characterized by crying, screaming, and other central nervous system symptoms. All outcomes were categorized as either treated and released (19 cases) or left against medical advice (2 cases).
- Only one case was reported for children 4 to less than 6 years of age. The case reported codeine and promethazine as suspect drugs, leading to fainting and an outcome of observation.
- Eight reports were for children age 6 to less than 12 years of age. Two reports were associated with phenylpropanolamine-containing products, two with opioid-containing antitussives, one with a toxicology screen positive for phencyclidine. Pain (one), large pupils (one), and palpitations (one) were reported in association with dextromethorphan and guaifenesin.

Overall, the limited amount of information available on these reports makes medical assessment difficult. Only two cases resulted in hospital admission and appear to be confounded or are associated with OTC medicines that are no longer available. In aggregate, these reports do not reveal serious or clinically severe events that might be associated with use of current OTC medicines in therapeutic doses. As seriousness, clinical severity, dose, and product names are neither consistently nor specifically reported, these data seem to provide a very limited basis for conclusions about the safety of the use of OTC cough and cold medicines in children when used as directed.

While these data provide a very limited basis for conclusions about the safety of OTC oral cough and cold medicines in children, we are mindful of FDA's expressed concerns regarding the data. On this basis, after consulting with FDA, CHPA member companies are voluntarily changing the labeling on oral OTC pediatric cough and cold medicines to state "do not use" in children under four years of age in the directions section of the label for OTC oral cough and cold medicines with labeling for use in children under 12 with monograph nasal decongestants, cough suppressants, or expectorants, but without antihistamines. These modified labels will continue to provide dosing information for children four years of age and older.

- For OTC oral cough and cold medicines with labeling for use in children under 12 that include antihistamines under the relevant OTC Review monograph, the existing, FDA-required direction to "ask a doctor" for children under 6 years of age should instead include the direction "do not use" for children under 4 years of age in the directions section of the label.
- OTC oral cough and cold products with labeling for use in children under 12 containing an antihistamine under the relevant OTC Review monograph should include the statement "do not use unless directed by a doctor" in place of the pre-existing direction to "ask a doctor" in children under 6 years of age in the directions section of the label.
- The warnings section of the label for <u>all</u> OTC oral medicines (whether for cough and cold, or allergy) with labeling for use in children under 12 containing an antihistamine under the relevant OTC Review monograph should include the warning: "Do not use to sedate children" or, alternatively, "Do not use to make a child sleepy."
- For OTC oral cough and cold medicines with labeling for use in children under 12, the principal display panel of products containing more than one active ingredient should include the name of all active ingredients, adjacent to the purposes.

Throughout the 2008-2009 cough and cold season, manufacturers are transitioning onto store shelves oral OTC pediatric cough and cold monograph products with these new labels.

3.6 Label Changes are Best Supported by Education

As discussed in Module 3 of this submission, CHPA has expanded its national education program aimed at parents, caregivers, and healthcare professionals to complement other programs, including these label changes. This education program and related publicity already shows promise in raising awareness – the first step in ultimately changing behavior.

As of the spring of 2008, 66% of caregivers of children up to 12 years of age said they had heard of public issues related to OTC cough and cold medicines for children [13]. This knowledge was higher (79%) in the sub-group with children under 2 years of age. Age 2 had been the original focus of much of the publicity surrounding FDA's October 2007 meeting, January 2008 public health advisory, and industry's initial label and pediatric focus steps through the voluntary withdrawal of oral cough and cold medicines designed for use in children under 2. A knowledge that there can be potential negative side effects is widespread, with almost two-thirds (64%) of caregivers reporting that they are aware of potential negative side effects of these medicines [13]. This awareness was also higher (70%) for caregivers of children under 2 years. Further, caregivers who are aware of the potential of side effects are more likely to agree with a statement regarding "the risks of using OTC cough and cold medicines for children under 2 are so great that I would never give a child in this age range an OTC cough and cold medicine" [13]. Findings such as these demonstrate the importance of label changes, education, and related publicity to mitigating risks based on the root causes of rare adverse events in young children.

3.7 Conclusion

Without OTC pediatric cough and cold medicines, there is a risk that parents could administer either adult formulations of OTC monograph cough and cold products or other alternatives, the safety and efficacy profiles of which are less well studied and less well documented than those of pediatric OTC cough and cold medicines.

To minimize these risks, we have started a multiyear education campaign aimed at encouraging the appropriate use of these medicines in accordance with voluntary label changes, which are underway now, to include "Do not use" for children under 4 in the directions section of the label. Other labeling changes are taking place as well.

3.8 Reference List for Question 3

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Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 4

FDA Question:

"Do the answers to the previous questions depend on the age of the pediatric patients? If so, how should age be considered in making regulatory decisions for these products?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

FDA Question 4. "Do the answers to the previous questions depend on the age of the pediatric patients? If so, how should age be considered in making regulatory decisions for these products?"

Response from the CHPA Pediatric Task Force

Age of pediatric patients has been taken into account in the CHPA comments to FDA's questions 1, 2, and 3. Specifically,

Question 1: The response to Question 1 describing the industry-sponsored pediatric research program is age-dependent by design. The response outlines general approaches to confirm or refine pediatric doses, to reaffirm effectiveness, and to further support safety of cough and cold ingredients in children. Although it is too early to choose an approach for each ingredient, the research pathways may have age dependant differences depending on the sensitivity and feasibility of instruments and endpoints for younger and older children. The CHPA Pediatric Task Force will consider the advantages, disadvantages, and scientific merit of various possibilities to support the effectiveness and safety of pediatric cough and cold medications, taking age of the children into account.

Question 2: The response to Question 2 regarding OTC status does not depend on age. Pediatric cough and cold products should be labeled for OTC use for all children over 4 years of age. Analysis of data from years of real-world use demonstrates that serious adverse events are very rare and parents can and do properly recognize and treat their children's colds. Pediatric cough and cold products are appropriate for self-medication in children and do not meet the criteria to be made available only by prescription.

Research shows that dosing errors and accidental ingestions are the leading causes of rare adverse events in young children. As a result, CHPA members who are the leading manufacturers of oral OTC pediatric cough and cold medicines are moving forward to implement of initiatives aimed at encouraging the appropriate use of these medicines, including directing parents and caregivers not to use these medicines in children under 4 years of age. The issues of accidental ingestions and dosing errors by caregivers apply in a similar way to prescription medicines

people use in their homes. Therefore, prescription status is not an adequate solution to these issues.

Question 3: The response to Question 3 regarding the use of adult products in the pediatric population does not depend on age. The 2008 Gallup Study of Concerns For Children's OTC Cold Medications conducted by Multi-sponsor Surveys, Inc., Princeton, NJ, asked a national sample of 759 caregivers of children 6 months to 11 years what they would do if OTC cough and cold remedies were not available. In response to this question, 40% of caregivers said they would use "natural, non-medication" remedies, and 24% of caregivers of children in all age groups said they would use OTC cough and cold medications formulated for older children and adults. These data indicate that misuse of adult products may occur if pediatric cough and cold products are no longer available.

Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 5

FDA Question:

"At the time the monograph was established, FDA routinely extrapolated safety and efficacy data from adults to children age 12 and over. Current PREA standards permit extrapolation of pediatric efficacy -- but not safety—based upon sufficient adult data. Does it remain appropriate to recommend in the cough and cold monograph that children 12 and over should receive the same dose of medication as adults, without requiring any additional studies in children in this age group? What additional safety and/or efficacy studies should be required in this age group?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 5

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"At the time the monograph was established, FDA routinely extrapolated safety and efficacy data from adults to children age 12 and over. Current PREA standards permit extrapolation of pediatric efficacy -- but not safety—based upon sufficient adult data. Does it remain appropriate to recommend in the cough and cold monograph that children 12 and over should receive the same dose of medication as adults, without requiring any additional studies in children in this age group? What additional safety and/or efficacy studies should be required in this age group?"

5.1 Position of the CHPA Pediatric Task Force

Cough and cold ingredients have a long history of therapeutic use in adults and children. As these ingredients are regulated under the monograph system, doses for adolescents 12 and over are the same as those for adults. As part of the industry's commitment, the CHPA member companies are conducting pharmacokinetic studies in children ages 2 to under 12 years to generate new data for eight cough and cold ingredients. In addition, most of these pharmacokinetic studies will also recruit adolescent subjects to generate pharmacokinetic (exposure) data for 12- to 17-year olds.

- If pharmacokinetic studies confirm that drug exposure is similar in adults and adolescents, then, concurrent with present practice, the same dose should be acceptable in adults and adolescents 12 years and older
- With comparable drug exposure, no additional safety and/or efficacy studies should be required in this age group because
    - the mechanisms of action, pharmacological effects, and clinical responses to cough and cold ingredients are substantially similar in adolescents and adults;
    - the metabolism and excretion mechanisms for these ingredients are similar in adolescents and adults, and effects due to hormonal changes and rapid growth and development are not of a magnitude to be clinically relevant; and
    - there is a long history of therapeutic use of these ingredients in adolescents and adults.

5.2 Current Regulatory Guidelines Address Adolescent Clinical Research

Confirming safe and effective doses for drug products is a key objective of both the pharmaceutical industry and regulatory authorities worldwide. The current FDA, and

International Conference on Harmonization (ICH) guidances attempt to balance the need for data with available science; methodologies of pharmacokinetic-pharmacodynamic modeling and simulation; and ethical considerations, such as subjecting a vulnerable population to additional testing if such testing is unlikely to add value to existing understanding.

The cough and cold ingredients that are regulated under the OTC monograph system have been available to consumers for a considerable length of time as single- and multiple-ingredient products. Some ingredients are also regulated under NDA. For example, pseudoephedrine and chlorpheniramine at OTC doses and dosing regimens, are approved under NDAs for products that are currently available by prescription (e.g., Allegra-D®) or nonprescription (e.g., Zyrtec-D®, Motrin® Sinus, Advil® Allergy Sinus). These were approved for use in adolescent populations either on the basis of additional data or because these ingredients have been considered generally recognized as safe and effective (GRAS/E) under the OTC monograph [1].

5.2.1 Regulatory Guidelines

FDA's "Exposure-Response Relationships" guidance [2] provides a framework for using pharmacokinetic-pharmacodynamic relationships from exposure-response studies of approved drugs, to support the use of these drugs in new target populations, such as pediatric populations for diseases whose pathophysiology is established and understood to be similar between adults and children. Such an approach can be helpful in establishing appropriate doses based on comparable exposures.

5.2.1.1 FDA Clinical Efficacy Guidance

The FDA guidance on providing clinical evidence of effectiveness [3] addresses the weight of evidence of effectiveness that can be demonstrated through pooling of data across studies. According to this guidance, demonstration of clinical efficacy in pediatric populations can rely on data in adults if the progression of disease is similar in adults and children and the metabolic pathways are similar. This guidance further highlights the need to balance the scientific and ethical aspects of drug development and evaluation by recognizing that, although clinical trials are limited in scope, drugs are approved and available for a wider population.

5.2.1.2 FDA Pediatric Guidance

The FDA guidance on pediatric drug clinical evaluations [4] describes special ethical, design, and scientific considerations for evaluation of drugs in children. It generally recommends that the safety and efficacy of new drugs be established first in adults, along

with elucidation of the mechanisms involved in absorption, metabolism, distribution and elimination of drugs. Once these are well understood, pediatric populations may be used for evaluation of drugs, although in general, the sample sizes may be small.

This guidance differentiates between the need for efficacy studies in adolescents versus younger children, especially infants below the age of 2 years, neonates and preterm infants, in whom differences in ontogeny from adults may be significant enough to affect the overall safety and efficacy of drugs. However, this guidance recognizes that the evaluation of efficacy in adolescents should use the same instruments and endpoints that are used in adults. Hence, many recent clinical safety and efficacy studies for prescription and OTC drugs have included adolescents in the adult efficacy studies. When adolescents are included in adult studies, their data are usually analyzed together with the adult data as the number of adolescents is small and usually does not justify a separate analysis. Unlike assessment of efficacy, safety evaluation of drugs in adolescent populations may have different objectives than studies in adults, as this age group is undergoing rapid development change and sexual maturation. Hence, safety evaluations of new drugs, especially those that are used chronically, may include specific endpoints related to growth and maturity, which may not be necessary for efficacy studies, if exposures and disease processes are similar.

5.2.1.3 ICH E11 Pediatric Guidance

The ICH E11 guidance [5] discusses the framework for pediatric drug development and how and when medicines need to be evaluated in pediatric populations. This guidance recognizes the special developmental aspects of adolescence (from 12 to 16-18 years of age), which is a period of sexual maturation, rapid growth, and neurocognitive development. The guidance emphasizes the need for evaluating the effects of chemical entities, especially those used chronically, on the growth and sexual maturation of adolescents.

5.2.2 Implications for Adolescent Clinical Research of Cough and Cold Ingredients

Cough suppressants, nasal decongestants, first-generation antihistamines and expectorants have been made available to consumers for common cold through the OTC monograph. These drug ingredients were included in the monograph by FDA as they were deemed GRAS/E upon the recommendation of an expert panel that reviewed the safety and efficacy data from multiple studies. Over the years since their inclusion in the OTC monograph, doctors and consumers have successfully relied on these ingredients to relieve cough and cold symptoms in adults and adolescents. Although there are significant data to show the effectiveness of cough and cold ingredients in adults, and some studies in adults have included adolescents of varying ages, separate studies in adolescents have not been

consistently reported. In most of the new industry-sponsored, pediatric pharmacokinetic studies, adolescents will be enrolled in order to characterize their pharmacokinetics. These additional data will be used to compare with systemic exposures in adults to confirm the current OTC doses for adolescents.

The FDA and ICH guidelines discussed above support the use of pharmacokinetic data for defining pediatric doses when exposures are similar, disease process is similar and the outcome of a therapy is expected to be comparable between adults and adolescents. There is recognition that large-scale, phase III-type controlled studies are not possible or even necessary in every population, especially pediatrics. The magnitude of variability in plasma concentrations may vary between age groups (eg. high variability in adolescents), but the plasma concentrations within the adolescents must be evaluated in the context of the therapeutic index of a drug and the benefit-risk profile from adults. The guidances require evaluation of clinical efficacy in pediatric populations when unique or novel indications are sought for pediatric populations, which is not the case for cough and cold ingredients [6].

Most OTC drug ingredients are recommended for short-term use. For diseases that require chronic treatment, consumers seek a doctor and are prescribed drugs that have long-term safety data available. Some of these prescription drugs may also include OTC ingredients that have long-term preclinical and clinical data, which support their chronic administration. For example, pseudoephedrine is approved for use as part of combinations of prescription drugs, in which, the pseudoephedrine doses are consistent with OTC doses eg. pseudoephedrine combinations with many antihistamine and pain-relieving medicines. Some of these approvals include short- and long-term toxicology data from multiple species and also reproductive toxicology data that support the safe use of these drugs and drug combinations across the range of pediatric and adult age groups [7,8].

A question unique to the adolescent population relates to the effect of hormonal changes around puberty on the pharmacokinetics of drugs. None of the OTC cough and cold ingredients have a documented gender effect in adults that warrants dose adjustments for either gender. Most of the planned or ongoing industry-sponsored, pharmacokinetic studies will generate additional data on drug exposure in adolescents to confirm the lack of significant effects on exposure as a result of hormonal changes. The therapeutic indications of cough and cold ingredients are the same in adults and adolescents. Hence, if exposures are similar, the clinical outcomes are expected to be similar as well. Data from adolescents enrolled as cohorts in clinical efficacy studies of some combination products that contain pseudoephedrine and chlorpheniramine, further support this expectation of similar clinical outcomes [9].

5.3 Adolescents and Adults are More Similar Than Different for Cough and Cold Ingredients

5.3.1 Metabolic Pathways for Cough and Cold Ingredients Are Mature Before Adolescence and Body Composition Differences are Unlikely to Warrant Dose Adjustments for Adolescents

Subtle differences in pharmacokinetics do not require a dosing adjustment for drugs that have a wide therapeutic index and a long history of safe use.

Adolescents, from 12 to 16 (or 18) years of age, range widely in body weight, size, hormonal milieu, growth, and development [10]. In most cases, puberty is complete by 16 to 18 years of age, but other organs, such as the brain, may continue to develop for a longer period of time [11]. Rapid developmental and hormonal changes may, in part, account for the observed high variability in drug exposures in the adolescent population [12]. For example, two 13-year-old females may have different hormonal levels based on their age at onset of puberty. Similarly two male adolescents may differ in their body fat composition, despite similar chronological ages. If the pharmacokinetics of a particular drug are affected by changes due to growth and sexual maturity, the pharmacokinetic data are still bracketed between those for the age groups that bracket adolescence i.e. the pharmacokinetics of drug X will be between those observed for 6- to 12-year olds and adults. These pharmacokinetic changes could be of clinical relevance for a drug with a narrow therapeutic index, such as digoxin [13], but may not be particularly relevant for drugs that have a large therapeutic index such as the OTC cough and cold ingredients.

In addition, as a matter of practical consideration, OTC ingredients are labeled for use by consumers for short durations and are self-dosed when they are ill. In a recent article Kennedy [10] reviewed the literature from the perspective of the pharmacokinetics of drugs being different during adolescence and found that for some drugs, Tanner staging (determines sexual maturation) may correlate better than chronological age with pharmacokinetic parameters. The data suggest that for several drugs, such as pravastatin, morphine, theophylline, and antipyrine, the clearances vary by 30% to 45% between pre- and post-pubertal subjects. However, this variability is within the realm of observed pharmacokinetic variability. For OTC ingredients it would not be practical or necessary to dose by Tanner stage. Unless there are marked differences in exposures between adolescents and adults that would be clinically important, dosing of these ingredients should remain as permitted by the monograph and be identical to adult doses that are generally recognized as safe and effective.

Metabolic pathways for cough and cold ingredients are fully mature before adolescence. Thus, body composition differences are unlikely to produce large enough pharmacokinetic differences to warrant adjustment of doses from those in the current paradigm.

Scientific data from various studies suggest that although there may be significant differences in the expression and function of different metabolizing enzymes between infants and adolescents, potential differences between adolescents and adults would not be outside the realm of variability in the pharmacokinetic parameters and may be within the acceptable range for the drug [14,15]. Most metabolic and clearance pathways are fully mature before adolescence (Table 5-1).

Table 5-1 Maturation of Metabolic and Clearance Pathways of Cough and Cold Ingredients [Adapted from 16]

Drugs	Class	Clearance Pathway		Time of Full Maturation
		Renal	Metabolic	
Pseudoephedrine	Decongestant	Major (55% to 75%)	Minor	Renal maturation complete by 2 years of age [17]
Guaifenesin	Expectorant	Minor	Major, Cytochrome P450s(CYPs)	Individual CYPs not identified
Dextromethorphan	Antitussive	Minor	Major (CYPs 2D6, 3A4, 2B6)	CYP 2D6 fully mature by 2 weeks after birth [18]; 2D6 polymorphic [19]; fully mature by age 2 years [20]
Chlorpheniramine	Antihistamine	Minor	Major (CYPs 2D6, 2C19)	CYP 2C19 fully mature by 10 years of age [21]
Brompheniramine	Antihistamine	Minor	Major (CYPs)	Individual CYPs not identified
Diphenhydramine	Antihistamine	Minor	Major (CYPs 2D6, 1A2, 2C9, 2C19)	CYP 1A2 fully mature by age 1 year; CYP 2C9 achieved adult values of maturity by 5 months of age [21]; CYP 2D6 fully mature by 2 weeks after birth [18]; CYP 2C19 fully mature by 10 years of age [21]
Phenylephrine	Antihistamine	Minor	Major (monoamine oxidases (MAO) [22], sulfation, glucuronidation [23])	MAOs mature by 2 years [24], glucuronidation between 3 to 10 years [25,26], sulfation unknown [25]
Doxylamine	Antihistamine	Major [27]	Minor (CYPs, glucuronidation)	Individual CYPs not identified

The review by Kennedy [10] suggests that hormonal changes can modulate the activity of drug metabolizing enzymes such as CYP1A2. However, similar changes may also be observed in adult subjects who take concomitant medicines such as hormonal contraceptives or other drugs that may affect the metabolic pathways by which the cough and cold OTC ingredients are metabolized and excreted. Hence, the scientific interest in characterizing the changes in pharmacokinetics as a result of physical and sexual maturation during adolescence must be balanced with rational and practical implications of subtle pharmacokinetic changes that are observed in the continuum of the population that may benefit from the drugs.

5.3.2 Mechanisms of Action and Pharmacological Response to Cough and Cold Ingredients are Likely to be Similar Between Adolescents and Adults

Cough and cold OTC ingredients provide symptomatic relief rather than treat the underlying cause of disease. The mechanisms of action of these drugs are unlikely to be different between adolescents and adults. Thus, it is reasonable to expect that similar exposures, and, by corollary, similar doses of cough and cold ingredients will be necessary in adolescents and adults to provide similar relief of symptoms.. This is different for drugs whose mechanism of action is dependent on maturation of receptors with chronological age or sexual maturity.

The wide therapeutic index for all cough and cold ingredients, coupled with a lack of any documented gender effect on the pharmacokinetics in adults, suggests that sexual maturity is unlikely to have an effect on the appropriateness of the current OTC monograph doses for adolescents. This premise may be confirmed with new systemic exposure data.

Pseudoephedrine is the most widely studied OTC cough and cold ingredient in the adolescent population, as it is available in single- and multiple-ingredient OTC cough, cold, and allergy medicines, including combinations with second generation antihistamines such as loratadine, fexofenadine, and cetirizine and with pain relief drugs such as naproxen and ibuprofen. Adolescents have been included in clinical efficacy and safety studies involving some of these combinations, and doses identical to adult doses have been evaluated and approved [8]. Although adolescent data from these have not been analyzed separately for efficacy due to small sample sizes, the safety data are comparable or better for this age group versus adults [8].

5.3.3 Supportive Adolescent Effectiveness and Safety Data for Cough and Cold Ingredients

Based on data for adolescents and adults in clinical efficacy and safety trials, different doses for adults and adolescents do not appear to be warranted [1,9,28,29,30,31]. Data from such studies are generally supportive of cough and cold ingredients having similar mechanisms and similar effects in adolescents and adults.

The industry-sponsored pediatric pharmacokinetic studies will provide additional exposure and pharmacokinetic data for cough and cold ingredients in adolescents. These data combined with existing safety and efficacy data may be used to further support dosing regimens in these populations.

5.4 Additional Safety and Efficacy Studies Not Needed in Adolescents for Cough and Cold Ingredients

Based on this review, the CHPA Pediatric Task Force asserts that sufficient data exist to justify the current dosing paradigm that is in use for adolescents for most OTC cough and cold medicines. Pharmacokinetic data from planned and ongoing pediatric studies that include adolescent populations will provide additional support for this paradigm. If research questions arise from the pharmacokinetic data that are clinically significant to warrant a dose adjustment, then a limited step-wise approach of clinical evaluation will be considered.

5.4.1 Confirmation of Doses of Cough and Cold Ingredients in Adolescents

Although significant efficacy data specific to adolescents are not available, the existing data for cough and cold ingredients in this population support the similarities of disease course and pharmacological responses with those in adults. These supportive efficacy data, when combined with emerging pharmacokinetic data, can be used to confirm current OTC doses. Even when no data are available in adolescents, it is still possible to make rational scientific decisions about doses based on interpolation of data from flanking age groups, i.e., younger than 12 years of age and older than 18 years of age.

5.4.2 Bridging Approach to Effectiveness

Through the use of modeling and simulation [32] and interpolation when data for adults and children under the age of 12 years exist, the effects of important intrinsic and extrinsic determinants on exposure can be evaluated and quantified in adolescents [2]. If such covariates as age, gender, body weight are not important in determining exposure, and the mechanism of action of a drug is independent of age (especially if the mechanism is similar in adolescents and adults), then even if subtle differences in exposures exist, these differences will not translate into a need for additional clinical trials or dose adjustment.

For most cough and cold ingredients, the pediatric pharmacokinetic studies being conducted by CHPA member companies include adolescents. These studies will provide valuable additional data that can be useful in the modeling and simulation for exposure response, where necessary. Through these efforts, emerging data will be used to confirm the current dosing paradigm for adolescents

5.5 Summary

The current dosing paradigm of using similar doses for adults and adolescents has been based on a combination of approaches that take into account maturation of metabolic and excretion pathways, similarity in symptoms for cough and cold between adolescents and adults and pragmatic dosing choices. Adolescence is a period of significant growth and sexual development, and these changes can result in a high degree of variability in pharmacokinetic data in adolescents. For cough and cold ingredients, there is no evidence to suggest that these differences are clinically significant and warrant changes in the current OTC dosing guidance or require additional efficacy and safety studies in this population. Emerging data from ongoing or planned pharmacokinetic studies in adolescents will be used to confirm the existing dosing paradigm.

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Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 6

FDA Question:

"What is the most appropriate method for determining pediatric doses that could be used as an alternative to the quarter- and half-dose assumptions used in the monograph? Should products be dosed by age, by weight, or both?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 6

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6 FDA QUESTION 6

"What is the most appropriate method for determining pediatric doses that could be used as an alternative to the quarter- and half-dose assumptions used in the monograph? Should products be dosed by age, by weight, or both?"

6.1 Position of the CHPA Pediatric Task Force

Traditionally, pediatric doses, including those for OTC cough and cold monograph ingredients, were based on empirical age-weight rules in the absence of pharmacokinetic and clinical trial data. Adult doses provided the reference point for therapy in children after doses were adjusted for body size. Since the late 1980s, pediatric clinical research has evolved significantly, with pharmacokinetic studies in children becoming more common, thus providing additional data to determine appropriate pediatric doses. In response to Question 6, the CHPA Pediatric Task Force maintains:

- To confirm or refine pediatric doses for children 2 to under 12 years, the most appropriate method should be scientifically based, using pharmacokinetic data, models, and simulation techniques to guide decisions.

- Pediatric doses of each OTC ingredient should be
  - based on pediatric pharmacokinetic data that show an adequate distribution of systemic exposure as that in adults,
  - linked to adult effectiveness data, and
  - supported by historical pediatric safety data.

- The appropriateness of pediatric OTC dosing schedules can be assessed using pharmacokinetic and simulation techniques to explore different numbers of weight and age divisions and, where appropriate, different dosing intervals.

- Importantly, the pragmatic aspects of pediatric OTC doses and labeling must be considered.
  - Leading scientific experts in academia and industry believe label dosing should be first based on weight and, if caregivers do not know the child's weight, then they would dose based on age.
  - For ease of consumer understanding and to avoid confusion and potential dosing errors, there may be a need to standardize weight and age divisions across OTC ingredients, where feasible.

- Doses for each ingredient should be suitable for single- and multiple-ingredient pediatric cough and cold medicines.

6.2 Determination and Selection of Doses For the Pediatric Population

6.2.1 Regulatory Guidances and the Prescription Drug Experience

In a recent overview of pediatric regulatory guidelines by Baber [1], he discusses whether they may help optimize dose selection for children. Baber concludes that these guidelines are adequate to cover modern and traditional approaches to drug development, but new guidelines can be modified as required. FDA has provided draft guidance on the design of pharmacokinetic studies in children [2], with one goal being the selection of doses for new drugs, and the EMEA also has a guideline on the role of pharmacokinetics in pediatric drug development [3]. As a general theme, the importance of pharmacokinetic data in determining pediatric doses is acknowledged in the overview and guidances, although pharmacodynamic, efficacy, and/or safety data often have a role when available.

In a review of pediatric studies that were submitted to FDA from July 1998 to October 2005, 23 out of 108 drugs with new or revised pediatric labeling had new pharmacokinetic information and/or dosing modifications due to the influence of differences in drug clearance in infants and children [4]. The authors of the review concluded that these label changes provide evidence that pediatric dosing should not be determined by applying weight-based calculations to the adult dose in all cases, but rather be supported or derived from pediatric pharmacokinetic data (e.g., drug clearance).

6.2.2 Pharmacometrics – A Contemporary Approach

Before the advent of pediatric pharmacokinetic, efficacy, and safety studies, doses for children were derived by scaling from adult doses. Biases and precisions associated with three scaling models based on body size have been reported for different pediatric age groups [5]. Comparison of predicted doses using these models with those in a national formulary found that no single method is suitable to scale doses across the entire pediatric population.

Pharmacometrics is an emerging science designed to inform decisions, such as dose selection, by conducting quantitative analysis of pharmacokinetic (and pharmacodynamic, efficacy, or safety) data [6]. Where desired, the analysis may include simulation techniques to examine different dosing regimens and future pediatric study designs. A survey of new drug applications from 2000 to 2004 found that the results of pharmacometric analyses influenced the outcomes of regulatory decisions for some applications, including the selection of pediatric doses and regimens for product labeling [7].

6.3 Integrate Historical and New Data to Determine Appropriate OTC Doses

6.3.1 General Approach for Cough and Cold Ingredients

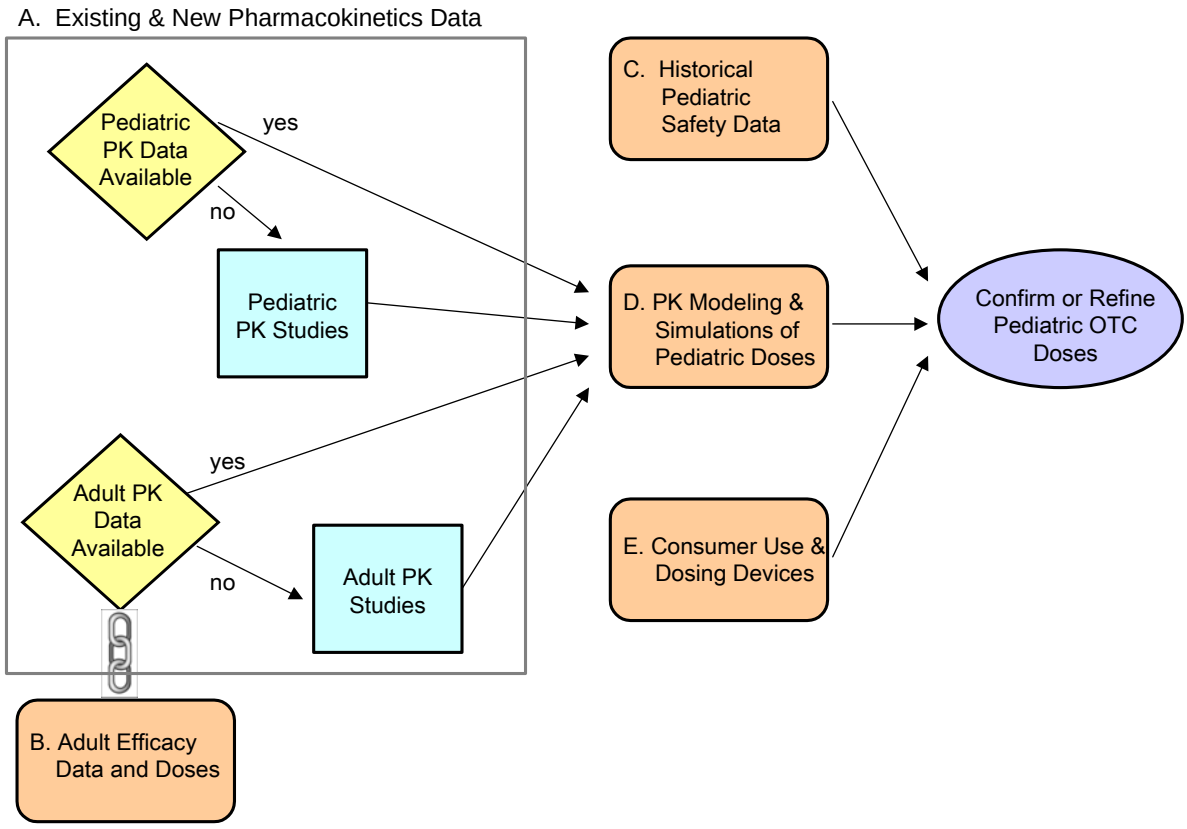
Pediatric doses for cough and cold ingredients have been used in children for many years and, as reviewed later in Section 6.4.1, the original OTC monograph doses were scaled from adult doses based on weight as a measure of the child's size. To confirm or refine the current doses for children 2 to under 12 years, the most appropriate method should be scientifically based using pharmacokinetic data. Depending on the ingredient, additional covariate models and/or simulation techniques may be used to guide dosing decisions. The CHPA Pediatric Task Force plans to use the current pediatric doses, if they are confirmed, in future efficacy studies. However, where necessary, the pediatric doses may be refined within the framework of the OTC cough and cold monograph.

Scheme 1 (as described previously in the response to Question 1) outlines data and pathways to confirm or refine pediatric OTC doses for the eight ingredients. The first step is the review of existing pharmacokinetic data in adults and children. As presented by CHPA member companies at the October 2007, FDA Advisory Committee meeting on pediatric cough and cold medicines [8], extensive pharmacokinetic data are available for pseudoephedrine in children, ages 2 to under 12 years, from four pediatric studies. Pharmacokinetic data are also available for chlorpheniramine in older children, ages 6 to under 12 years. For the other ingredients lacking such data, the CHPA Pediatric Task Force has committed to conduct seven single-dose pediatric pharmacokinetic studies, which have been planned or are underway recruiting children.

Historical pharmacokinetic data in adults from one or more studies may be pooled with pediatric pharmacokinetic data in a modeling and simulation analysis to explore a range of appropriate pediatric doses and dosing intervals [9]. Where pharmacokinetic data for these cough and cold ingredients exist in adults, there is no need to conduct additional adult pharmacokinetic studies for comparison of systemic exposures.

As shown in Scheme 1, new pediatric and historical adult pharmacokinetic data will be pooled under a pharmacokinetic analysis plan. The first objective of this plan would be to describe the pharmacokinetics of the cough or cold ingredient after oral administration in children and adults, including the influence of subject covariates (e.g., age and body weight) on the intersubject variability. The second objective would be to assess the current pediatric OTC dosing schedule using pharmacokinetics, models, and/or simulation techniques. These will help identify potential dosing rules in children that provide a distribution of systemic exposures comparable to those observed for the adult dose or multiple-dose regimen associated with efficacy.

Scheme 1. Integrate Historical and New Data to Confirm or Refine Pediatric Doses



In addition to modeling and simulations, other inputs into the selection of pediatric doses include historical safety data in children and prior exposure-response data in adults. Generally, the therapeutic window established in adults is a reasonably good predictor of pediatric response. The pragmatic aspects of OTC dosing, namely, ease of consumer understanding and suitability for single- and multiple-ingredient products, will also be considered. The pragmatic aspects of dose selection are discussed in Section 6.5.

In summary, the strategy for assessing the adequacy of different OTC pediatric dosing schedules for children, ages 2 to under 12 years, will be based on overall consideration of

- drug disposition
- number of weight-age divisions
- single- and multiple-dose drug exposure
- dosing interval
- ranges of systemic exposure associated with adult efficacy and safety
- pediatric safety data
- pragmatic aspects of OTC dosing

6.3.2 Refinement of Pediatric OTC Doses Within Framework of Monograph

The CHPA Pediatric Task Force plans to use the current pediatric OTC doses in future efficacy studies where they are confirmed by pharmacokinetics, models, and/or simulation techniques. Pragmatic aspects of consumer use will also be considered. As shown in Table 6-1, all eight ingredients, except phenylephrine, have more than one dose or dosing interval available to compare with adult systemic exposures.

Table 6-1 Monograph Dosages for OTC Cough/Cold Ingredients (21 CFR Part 341)

Ingredient	Children 2 to < 6 Years of Age		Children 6 to < 12 Years of Age	
	Dose	**Dosing Interval**	**Dose**	**Dosing Interval**
Brompheniramine[a]	1 mg	every 4 to 6 hours	2 mg	every 4 to 6 hours
Chlorpheniramine[a]	1 mg	every 4 to 6 hours	2 mg	every 4 to 6 hours
Diphenhydramine[a]	6.25 mg[b] 6.25 mg[c]	every 4 hours every 4 to 6 hours	12.5 mg[b] 12.5 to 25 mg[c]	every 4 hours every 4 to 6 hours
Doxylamine[a]	1.9 to 3.125 mg	every 4 to 6 hours	3.75 to 6.25mg	every 4 to 6 hours
Dextromethorphan	2.5 to 5 mg 7.5 mg	every 4 hours every 6 to 8 hours	5 to 10 mg 15 mg	every 4 hours every 6 to 8 hours
Guaifenesin	50 to 100 mg	every 4 hours	100 to 200 mg	every 4 hours
Phenylephrine	2.5 mg	every 4 hours	5 mg	every 4 hours
Pseudoephedrine	15mg	every 4 to 6 hours (total of 4 doses)	30 mg	every 4 to 6 hours (total of 4 doses)

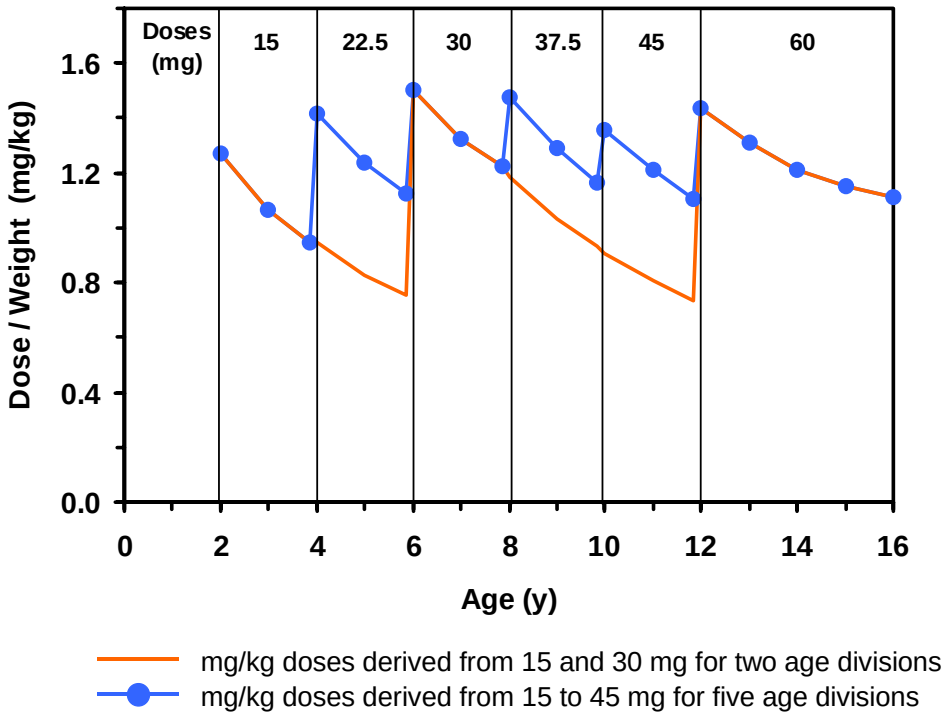
a: professional monograph dosing for children ages 2 to < 6 years
b: dose and dosing interval for the antitussive indication
c: dose and dosing interval for the antihistamine indication

If necessary, the pediatric OTC doses may be refined within the framework of the monograph. Two potential approaches to refine pediatric doses within this framework were presented by CHPA at the October 2007 FDA Advisory Committee meeting on pediatric cough and cold medicines [8], using pharmacokinetic data on pseudoephedrine to illustrate them.

One approach is to reaffirm the effectiveness of the current pediatric OTC doses at one of two dosing intervals that are permitted by the monograph. For example, pharmacokinetic modeling and simulations may show that the distribution of systemic exposures would be comparable at current OTC doses if they are given every 4 hours in children and every 6 hours in adults. Alternatively, the distribution of systemic exposures in children may be comparable with adults at the higher of two permitted pediatric doses where available.

Another potential refinement in a dosing schedule is the inclusion of doses for a greater number of weight-age divisions, such that children from 2 to under 12 years will receive a consistent range of "mg/kg" doses. Pharmacokinetic modeling and simulations will explore different numbers of divisions that provide a distribution of systemic exposures across age groups, including adults, and that would be supported by the long history of safe use at monograph doses. Figure 6-1 illustrates a potential dosing schedule for pseudoephedrine. It is shown as an example, but the pharmacokinetic modeling and simulation analysis plan for this ingredient is still being drafted. Results of the subsequent analysis will be reviewed to determine whether there is the need for any dose refinement.

Figure 6-1 Additional Weight-Age Divisions, Using Pseudoephedrine as an Example, Result in Less Spread of MG/KG Doses by Age (2 to < 12 years)



6.3.3 Defining Dosing Rules With Pharmacokinetic Data and Simulations

6.3.3.1 Dosing Rules Based on Body Size

Recently, Anderson and Holford have published an extensive and timely review on mechanism-based concepts of size and maturity in pharmacokinetics that are relevant to the determination of pediatric dosing [10]. Size models play a significant role in determining

pediatric pharmacokinetic parameter estimates and, consequently, drug doses for children, but they have limitations [5,10,11].

Body weight has been used most commonly to scale for size in dosing rules, although it is recognized that there is a nonlinear relationship between weight and dose. Clark's Dosing Rule, which assumes a linear relationship between weight and dose, was originally used to define the current OTC pediatric doses of cough and cold ingredients. Although the weight-based model tends to give the best estimates of infant doses based on precision and bias, it tends to underestimate doses across the entire pediatric population [5]. Because drug clearance is reduced in infants due to incomplete development, the use of the linear "per kilogram" dosing model often predicts appropriate doses by coincidence [10]. This is consistent with pharmacokinetic data that show the ratio of children and adult body weight with no exponent as the best predictor of drug clearance for children 1 year old or younger [12].

Generally, children require or tolerate a larger dose expressed as mg/kg than adults [11]. Normalization of clearance of metabolically eliminated drugs based on "per kilogram body weight" may suggest that children between 1 and 6 years of age have equal or higher clearance than adults when, in fact, they do not [10,11]. Holford [13] pointed out this misconception several years ago, but the practice of weight-normalization clearance across the entire pediatric population continues.

Another dosing rule based on scaling for differences in size between children and adults incorporates body surface area as a percentage of the adult dose. Body surface area is the basis for defining the current OTC pediatric doses of analgesic ingredients in the internal analgesic monograph. For children from about 5 to 12 years of age, the body surface area model predicts doses that are more precise and less biased than those derived from body weight [5].

Allometric size adjustments to pharmacokinetics data provide a more mechanistic, physiologically based approach that can distinguish the effect of size from that of other covariates that show a high degree of co-linearity [9]. The allometric "3/4-power" model has been shown to be useful for normalizing a large number of physiological parameters across species and age groups, and may be useful as a pediatric dosing rule based on drug clearance [11]. Allometry decouples size from age, allowing a consistent approach to describing data in children and adults [10]. However, due to the nature of the exponents of allometry, one single exponent does not predict drug clearance in children across all age groups [12]. Yet, in children after age 5, data show that a dosing rule based on one of the three exponents (0.75, 0.80, and 85) will achieve a reasonably good prediction of clearance [12].

6.3.3.2 Future Pediatric Dosing Schedules for Cough and Cold Ingredients

At this time, the CHPA Pediatric Task Force has contracted with an external pharmacokinetic modeling expert to develop a data analysis and modeling plan to confirm or refine the pediatric doses of pseudoephedrine. This plan will consider allometric and empiric models to quantify the effect of covariates on pediatric pharmacokinetic data from which potential dosing rules will be defined. Although the allometric approach is more mechanistically and physiologically based, the empiric approaches are a more pragmatic tool to overcome large size differences in the pediatric population [9].

Current pediatric doses and dosing intervals permitted for cough and cold medicines under the monograph (shown previously in Table 6-1) provide latitude within which to assess pharmacokinetic data and to define dosing rules that could be broadly applied across ingredients. Once potential dosing rules are defined, they would be translated into a simplified OTC pediatric dosing schedule based on weight and age, as appropriate.

As highlighted previously in Section 6.3.1, the strategy for assessing the adequacy of different pediatric OTC dosing schedules for children, ages 2 to under 12 years, will be based on overall consideration of drug disposition, number of weight-age divisions, single- and multiple-dose drug exposure, and dosing interval. Prior qualitative and quantitative information on ranges of systemic exposure associated with adult efficacy and safety, as well as pediatric safety data, will also be considered in the determination of appropriate doses.

6.4 Consideration of Weight-Age Algorithm for Pediatric OTC Labeling

6.4.1 Regulatory History of Pediatric OTC Dosing

In the *Federal Register* of September 9, 1976, FDA published a proposed rule for the OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (CCABADP) monograph that included pediatric dosages for many OTC cough and cold ingredients based on recommendations of the Advisory Review Panel [14]. The Panel stated that pediatric dosage calculations for infants and children were traditionally based on body surface area, weight, or age of a child as a proportion of the “usual adult dose”. The panel recognized that determining pediatric dosages based on age, although convenient, might be the least reliable method because of the large variation in weight of children at a specific age. However, the panel stated that, because the OTC ingredients have a wide margin of safety, children’s dosages based on age would be the most reasonable because they would be most easily understood by the consumer. After consultation with a special panel on pediatric drug therapy, the Advisory Review Panel recommended children’s dosages for OTC cough and cold ingredients based on a fraction of the adult dose. For the majority of

ingredients in the CCABADP monograph, doses for children 2 to under 6 years were recommended to be one-quarter of the adult dosage, whereas doses for children 6 to under 12 years were recommended to be one-half of the adult dosage.

In the *Federal Register* of July 8, 1977, FDA published a proposed rule for the OTC Internal Analgesic and Antirheumatic Drug Products Monograph that included pediatric dosages for OTC internal analgesic drug products, based on recommendations of the Advisory Review Panel [15]. In determining the appropriate basis for pediatric dosages, the panel discussed the relationships both between a child's body surface area and age and between a child's body weight and age. Noting that the relationship between body surface area and age for children ages 3 to 12 years is linear and the relationship between body weight and age is nonlinear after 7 years of age, the panel based its pediatric dosage recommendations for internal analgesics upon the daily dosage of 1.5 grams/meter^2 body surface area for each age. The panel recommended a standard adult dosage unit of 325 mg and a standard pediatric dosage unit of 80 mg for both acetaminophen and aspirin. Additionally, the panel recommended more finely divided age breaks for the pediatric dosing schedule for the internal analgesics of 2 to under 4 years; 4 to under 6 years; 6 to under 9 years; 9 to under 11 years; and 11 to under 12 years of age.

In the *Federal Register* of June 20, 1988, FDA published a Notice of Intent and Request For Information on Pediatric Dosing Information for OTC Human Drugs, stating that the agency was considering proposing a rule concerning dosing information on labeling for OTC drugs for use in children under 12 years of age [16]. In this notice, FDA reviewed the Advisory Review Panel recommendations described above, as well as comments that were submitted to the docket concerning the pediatric dosing schedule for cough and cold ingredients. FDA received comments from four manufacturers and CHPA, then known as The Proprietary Association, requesting that the pediatric dosages for cough and cold products be revised to provide a greater subdivision of age ranges for children under 12 years of age that would more closely approximate weight-based dosages. The revised dosages were based on a standardized pediatric dosing unit of one-eighth the adult dose and standardized dosing age ranges. This proposed dosing scheme, which would provide sufficient flexibility in dosage schedules by basing them on age and weight, eliminated inconsistencies between the internal analgesic and cough and cold drug products dosing schedules.

In the 1988 notice, FDA also published a recommendation received in 1986 from the American Academy of Pediatrics (AAP), which encouraged the agency to accept the recommendations submitted to the CCABADP docket for more weight-based, age-related dosage ranges for children's dosages of OTC drug products. Several comments to the docket stated that a benefit of having weight-related dosages optionally available on the label is that they can be used when a child's weight is known, especially for children who

are very large or very small for their age or are approaching the usual age break for a given dosing schedule.

FDA convened a meeting of the Nonprescription Drugs Advisory Committee (NDAC) on January 13, 1995, to discuss pediatric dosing of OTC drug products. At this meeting, the dosing schemes described above were presented to the NDAC committee for consideration. Additionally, the chairperson of the Committee on Drugs of the AAP provided the position that the use of body weight was AAP's preferred basis of drug dosing for OTC products.

NDAC, when asked to vote on what was the preferred basis for determining OTC systemic pediatric dosages and labeling, voted unanimously that weight first, then age was the preferred basis. Additionally, the majority of NDAC members voted that the current dosing approach of one-half the adult dose for children 6 to under 12 years and one-quarter the adult dose for children 2 to under 6 years was not an adequate way to label these OTC products for pediatric use.

6.4.2 FDA Endorsement of Weight then Age (Fact Sheet)

A "Checklist for Choosing Over-the-Counter (OTC) Medicine for Children," available on FDA's website [17], advises parents and caregivers to use a child's weight to find the right dose of medicine on the Drug Facts label. If the caregiver does not know the child's weight or the Drug Facts label does not show a dose by weight, caregivers are instructed to use age to find the right dose.

6.5 Pragmatic Considerations of Pediatric OTC Dosing Instructions

6.5.1 Pediatric Dosing for Cough and Cold Medicines by Age, Weight, or Both

The statutory criterion for OTC labeling is the demonstration that labeling can be written for consumers to use a product safely and effectively without a prescription. The label must convey the core communication objectives of safe and effective use of the product by consumers. This would include the ability of a parent to dose a child. FDA's current advice for caregivers (parents or guardians) on OTC dosing is to use weight and, if the child's weight is not known, then to use age [17]. Current pediatric monograph dosing instructions for OTC cough and cold ingredients are based on a dose for each of two age groups: children ages 2 to under 6 years and 6 to under 12 years. FDA's proposed approach for dosing instructions for OTC analgesic ingredients is based on five age divisions, and weight ranges are included on the dosing chart. The realities of self-medication and consumer behavior should be carefully considered if a change in the dosing paradigm for OTC cough

and cold ingredients is contemplated based on the assessment of new pediatric pharmacokinetic data.

A dosing chart for cough and cold ingredients based only on weight is not recommended by the CHPA Pediatric Task Force, because a significant proportion of parents or caregivers, when asked, are unable to state their child's weight, even when the physician had just stated the child's weight during the visit [18]. Doctors, nurses, and parents are equally poor at estimating pediatric weights [19]. Nevertheless, a study of the accuracy of doses parents used for antipyretic medicines found that 51% of children had been given an inaccurate dose of medication [20]. Parents who stated that medication dosage was based on their child's weight were less likely to give an inaccurate dose of medication (relative risk = 0.71, $P < 0.03$). The survey had asked caregivers about the quantity and frequency of antipyretic use prior to the emergency department visit, the source of information used to determine dosage, and which factor (e.g., age, sex, height, weight, height of fever, and severity of illness) they considered most important in determining the correct dosage of medication.

If dosing charts for cough and cold ingredients are modified to include weight on the basis of new pediatric pharmacokinetic data and modeling, they should also maintain an appropriate dose based on the child's age, because caregivers may not know the child's weight at the time of dosing. Also, when caregivers estimate doses, studies have shown that underdosing may result in weight-based dosing situations. They may give a dose that was used previously in the same child, not realizing that a higher dose is needed as the child has grown older and gained weight over time [21,22,23].

Including dose recommendations by both weight and age in future dosing charts for cough and cold pediatric medicines would be a shift from the more simplistic chart of doses for only two age groups. One study evaluated the ability of caregivers to correctly interpret a pediatric dosing chart for a liquid [24]. Subjects were shown a dosing chart that had dosing listed by both age and weight and contained a note that dosing by weight is more accurate. Participants were asked to indicate the correct dose for two children. In one example the child's age and weight matched on the chart, and in the second example the age and weight were discordant (e.g., a higher weight for the child's age). The pediatric dosing chart was correctly interpreted by 87% of the participants for both examples. Although instructed by the note that dosing by weight is more accurate, 12% of those surveyed gave the dose based on the child's age rather than weight when the age and weight of the child were discordant.

6.5.2 Recommend Harmonized Dosing Charts for Cough and Cold Ingredients

The CHPA Pediatric Task Force recommends that future pediatric dosing schedules for cough and cold ingredients be suitable for single-ingredient and combination formulations. Given the scope and complexity of the industry-sponsored research program that includes eight cough and cold ingredients, decisions on pediatric dosing for one ingredient may have an impact on dosing choices for the other ingredients. This situation is especially important for OTC ingredients that may be combined to treat different sets of symptoms of the common cold.

Deliberations on pharmacokinetic data and potential dose refinements for individual ingredients should be undertaken among stakeholders in the context of all ingredients such that appropriate pediatric dosing schedules can be implemented across single- and multiple-ingredient medicines. For most drugs with therapeutic indices of more than 50%, some dose approximation can often be made within the window of known safety [25]. Because the cough and cold ingredients have a wide therapeutic index, we should strive to define potential dosing rules from pharmacokinetic data that translate into an uncomplicated OTC dosing schedule for children, one that could be readily understood by caregivers. Current pediatric doses and dosing intervals permitted for cough and cold medicines under the monograph (shown previously in Table 6-1) provide latitude within which to harmonize or create flexible dosing schedules across ingredients.

6.6 Summary

To confirm or refine pediatric doses for children 2 to under 12 years, the most appropriate method would be scientifically based, using pharmacokinetic data, models, and/or simulations to guide decisions. Pediatric doses of each OTC ingredient should be based on pediatric pharmacokinetic data that show adequate drug exposure as that in adults, be linked to adult effectiveness data, and be supported by historical pediatric safety data. Importantly, the pragmatic aspects of communicating age and weight for OTC pediatric doses must be considered, as must harmonized dosing schedules that are suitable for single- and multiple-ingredient pediatric medicines.

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Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 7

FDA Question:

"There are monographs for topical and intranasal ingredients to treat the common cold. Should these monographs be considered in a similar fashion to the oral cough and cold products? Are the answers to the previous questions different for any subcategories of cough and cold medicines (e.g., topical or intranasal products)?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 7

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"There are monographs for topical and intranasal ingredients to treat the common cold. Should these monographs be considered in a similar fashion to the oral cough and cold products? Are the answers to the previous questions different for any subcategories of cough and cold medicines (e.g., topical or intranasal products)?"

7.1 Position of the CHPA Pediatric Task Force

It is the position of the CHPA Pediatric Task Force that topical and intranasal ingredients should not be considered in a similar manner to orally ingested cough and cold ingredients. Topically administered cough and cold products offer an alternative delivery system direct to the symptomatic organ in significantly lower doses and demonstrate a lower systemic exposure to the active ingredient than that of orally administered products. The CHPA Pediatric Task Force's position in response to Question 7 is supported by the following conclusions drawn from a comprehensive review of the medical literature, the National Poison Data System (NPDS) and the FDA Adverse Event Reporting System (AERS):

- The monographs for topically applied nasal decongestants should not be considered in a similar manner than the ones for the oral nasal decongestants for two reasons:
    - Because of lower doses administered as well as the intranasal delivery route, the systemic exposure is markedly lower than the oral nasal decongestants.
    - The efficacy of intranasally applied decongestants results from a topical effect, i.e. from direct contact with the nasal mucosa, and not from systemic activity.
- The adverse event profile of topically administered products is favorable and consistent with the low systemic exposure of the ingredient. Current review of the safety profile supports the continuation of the Generally Recognized as Safe and Effective (GRASE) classification.
- Oral products should be evaluated independent of topical, intranasal or other alternative applications as there are no other relevant subcategories of cough and cold products that present similar efficacy or safety characteristics.

7.2 Active Ingredients of Common OTC Intranasal Products

The most common active ingredients in OTC intranasal products are phenylephrine, oxymetazoline and xylometazoline. Intranasal products that contain phenylephrine, oxymetazoline or xylometazoline have a long and safe history of use worldwide as an OTC nasal decongestant for more than 25 years. Currently, use of these products in the United States is regulated under the FDA Code of Federal Regulations, Part 341—Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use [1]. Phenylephrine, oxymetazoline and xylometazoline are currently classified in the monograph as

GRASE. The original classification of these drugs was done by FDA during the OTC monograph review process that began in 1972 with the final monograph for nasal decongestants published in 1994 [1]. The table below outlines the monograph pediatric dosing for these ingredients:

Table 7-1. Monograph Dose of Phenylephrine, Oxymetazoline and Xylometazoline by Age

Drug Solution →	Phenylephrine			Oxymetazoline		Xylometazoline
	0.25%	0.125%	oral	0.05%	0.025%	0.05%
6 to <12 years	2-3 drops or sprays every 4 h (mg not specified)	Not specified	5 mg every 4 hours (≤30 mg in 24 h)	2-3 drops or sprays every 10-12 h (mg not specified)	Not specified	2-3 drops or sprays every 8-10 h (mg not specified)
2 to <6 years	Consult a doctor	2-3 drops or sprays every 4 h (≤0.135 mg/3 drops or sprays)	2.5 mg every 4 h (≤15 mg in 24 h)	Consult a doctor	2-3 drops or sprays every 10-12 h (≤0.027 mg/3 drops or sprays)	2-3 drops or sprays every 8-10 h (≤0.054 mg/3 drops or sprays)
<2 years	Consult a doctor	Consult a doctor	Consult a doctor	Consult a doctor	Consult a doctor	Consult a doctor

7.3 Pharmacology of Nasal Decongestants and Pediatric Clinical Trials

Nasal congestion is a symptom experienced by the general population, including young children, that results mostly from common colds and upper respiratory allergies. It is considered the most bothersome and difficult to treat of the symptoms of rhinitis. The clinical picture of the common cold is similar in children and adults, because the main symptoms of nasal congestion, rhinorrhea, sneezing, and cough are more representative of a clinical syndrome rather than a specific etiology. Likewise, the clinical picture of allergic rhinitis is similar in children and adults with manifestation of nasal symptoms of rhinorrhea, nasal itching, sneezing, and nasal congestion.

The nasal decongestants, phenylephrine, oxymetazoline, and xylometazoline, are sympathomimetic agents. These intranasal agents produce both direct and indirect sympathomimetic effects [2], but the dominant effect is direct selective agonist at α1-adrenergic receptors. At the current OTC intranasal dose, these agents do not have agonist effect on the β-adrenergic receptors. Stimulation of the α1-adrenergic receptors located on capacitance blood vessels of the nasal mucosa (postcapillary venules) results in vasoconstriction, decreased blood volume and a decrease in the volume of the nasal mucosa (nasal decongestion) [3].

7.3.1 Phenylephrine

7.3.1.1 Low Systemic Exposure with Intranasal Phenylephrine

Phenylephrine exists in both oral and intranasal forms. Intranasal products generally contain only 0.25% active ingredient leading to maximum daily doses of 2.1 mg phenylephrine. The usual oral decongestant dosage of phenylephrine hydrochloride for children 6 to less than twelve years of age is 5 mg of phenylephrine hydrochloride every 4 hours leading to maximum daily dosage of 30 mg. The maximum daily dose from intranasal phenylephrine products is more than 10 times lower than what is used in oral forms (Table 7-1). Bioavailability of phenylephrine following oral administration is 38% relative to IV administration [4]. Despite this relatively low bioavailability, the systemic levels following usage of a topical nasal product would still be similarly lower than that of oral administration. Although the dose administered via intranasal application is significantly smaller than oral administration, efficacy is not compromised due to its target delivery to the nasal site.

7.3.1.2 Published Pediatric Clinical Trials with Phenylephrine

There are published randomized controlled trials that illustrate the efficacy of intranasal phenylephrine using both subjective and objective measures. Johnson AE (1970), an observation study with case report forms, studied 56 children with severe to moderate bronchospasm aged 4 to 19 years who received phenylephrine 0.5% in nasal inhalational therapy followed by an oral inhalation of an epinephrine derivative [5]. Nasal obstruction was initially relieved for two to three hours, however as the intervention continued, relief time lengthened until the nasal block was cleared. This clearance remained until the next exposure to a nasal antagonist. Johnson also found a decrease in edema, less hypertrophied turbinates, relief or the absence of headache, increase in nasal discharge, and a decrease in cough. Epistaxis was not reported and “rebound” phenomenon was seldom experienced. In a randomized, controlled clinical trial, Vogt FC (1966) studied 100 pediatric patients with median age between one and two years [6]. Patients received either 0.25% phenylephrine or 0.25% phenylephrine plus 0.02% nitrofurazone. The majority of parents rated both treatments as excellent or good in the treatment of symptoms.

7.3.1.3 Additional Supporting Evidence of Pharmacological Response to Phenylephrine

Additional evidence of phenylephrine’s vasoconstrictive action on nasal mucosa in children is corroborated by its use as a topical decongestant with acoustic rhinometry to assess nasal function for clinical purposes. Acoustic rhinometry has become a valuable tool for assessment of nasal function for both clinical and research purposes. Most clinicians take measures separately at baseline and after appropriate decongestion or shrinking of the mucosa by sympathomimetic agents [7].

Topical phenylephrine has been used to decongest nasal mucosa in adults and children as part of diagnostic procedures and clinical assessments with acoustic rhinometry. For example, in a clinical study of 31 children, ages 5 to 14 years, with adenotonsillar hypertrophy [8], the clinical investigators were able to report that adenoidectomy and tonsillectomy reverse the congestion of the inferior turbinate of the nose. This was shown by rhinometry before and after decongestion with 1% phenylephrine spray conducted before and after surgery. These data are not intended to extrapolate efficacy to orally administered drug, but rather they further support the underlying assumption of substantially similar repose to pharmacological intervention with nasal decongestants among children and adults.

7.3.2 Oxymetazoline and Xylometazoline

7.3.2.1 Low Systemic Exposure with Intranasal Oxymetazoline and Xylometazoline

Oxymetazoline and xylometazoline are topical decongestants. Oxymetazoline-containing products are prepared as either 0.05% or 0.025% solution and xylometazoline as a 0.05% solution (Table 7-1). In topical nasal products containing xylometazoline or oxymetazoline, maximum daily doses are below 1mg of drug per day. There are no data on comparison with oral application of these ingredients because such products do not exist. Limited published bioavailability data for these drugs exists [9], however, non-detectable plasma levels of xylometazoline have been reported following nasal application. The levels were below the limit of detection because of the very small doses used and are not only the result of limited absorption. With therapeutic doses this low, few adverse effects are expected. Despite a dose of less than 1 mg per day, delivered topically to the nasal mucosa these drugs remain efficacious.

7.3.2.2 Published Pediatric Clinical Trials With Intranasal Oxymetazoline and Xylometazoline

Efficacy studies for oxymetazoline and xylometazoline are more abundant both in quantity and quality than those for phenylephrine. Study populations, methods and key endpoints are often well described and support the efficacy of these drugs in children when applied intranasally. In a double-blind active controlled trial, Neffson [10] studied oxymetazoline use in 42 children age nine months to five years. Intranasal oxymetazoline (0.025%) was administered for one to two weeks without report of adverse events by the physicians, parents, or children. Efficacy was evaluated by decreased congestion and shrinkage of nasal membranes as well as parental observations of decongestive effects. Cohen et al [11] studied 30 children age four to ten years with chronic allergic rhinitis who received oxymetazoline 0.025% solution three times daily for two weeks. Nasal flow resistance decreased with oxymetazoline therapy as compared to children free of nasal disease or anatomic obstruction. Blood pressure was monitored throughout the study and no change was detected with the use of oxymetazoline. Finally, in a randomized double-blind active controlled study, Sengelmann [12] compared the use of 0.25%

phenylephrine to 0.05% xylometazoline for the treatment of a “stuffy nose” in 44 children age five years or younger. Preparations were rated as equally effective, helpful and acceptable by the parents of these children noting that no side effects of consequence were reported for either preparation.

7.4 Similarity of Pharmacological Response Between Adults and Children

Despite limitations of the published pediatric clinical trials, these trials provide clinical evidence of a pharmacological response to nasal decongestants in children that could support the assumption of a substantially similar response to those observed in the adult population. Nasal congestion is a symptom experienced by children and adults in common colds and allergic rhinitis. It is caused by engorgement of specialized capacitance sinusoids in the nasal epithelium due to local vasodilation, and also by increased vascular permeability and stimulation of nerves. This localized physiologic response of the nasal mucosa is essentially similar in children and adults independent of whether the inciting trigger is an infectious agent, allergen, or irritant.

Compared with adults, the prevalence of nasal congestion associated with the common cold may be higher [13]. The current body of epidemiological and clinical data supports the assumption that nasal congestion in children has sufficiently similar disease progression and pathophysiology as in the adult population. Based upon the available data, it is reasonable to assume that the response to nasal decongestants (or clinical outcome of therapy) is likely to be substantially similar between adults and children, especially children older than 2 years.

7.5 Additional Evidence to Support the Position that Intranasal and Oral Products Should be Independently Evaluated

Due to the limited data on efficacy and sometimes safety data of monograph drugs, we searched for a modern day comparison to further demonstrate why oral products should not be considered in the same manner as intranasal products with the same active ingredients. A recent example is the introduction of intranasal corticosteroids. Studies indicate that oral delivery of corticosteroids results in 80% to 100% bioavailability yet intranasal exposures result in 0.1% to 50% bioavailability depending on the compound [14]. Additionally, adverse events are minimized with intranasal corticosteroid exposure compared to the same active ingredient administered orally. These data indicate lower bioavailability, lower systemic exposure and a more favorable safety profile supporting that these drugs work more efficiently when applied directly to the organ rather than through oral administration. Based upon these differences, it would be prudent to evaluate the oral and intranasal products independently even though they contain the same active ingredient.

Overall, the difference in bioavailability, systemic exposure, dosing and safety between oral and intranasal products is substantial. To treat these products in a similar fashion would be difficult to do methodologically, physiologically and clinically and is therefore discouraged.

7.6 Safety Characterization Using a Comprehensive Systematic Review of Multiple Data Sources

A comprehensive review of safety information from three data sources was performed to characterize the safety profile of the most common intranasal cough and cold ingredients including phenylephrine, oxymetazoline or xylometazoline in children age less than twelve years. The data sources included the medical literature, the National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC) and the Adverse Event Reporting System (AERS) of FDA. The purpose of the safety characterization is to evaluate the current GRASE classification of intranasal drugs using modern data.

Diverse data sources were selected to increase the likelihood of identifying rare events by capturing all potential reporting data. The data sources vary in methodology, detection and reporting which allows for cases missed in one system to be detected in another. For example, prospective study reports would only be found in the medical literature while NPDS and AERS only include spontaneous reports. Overlap may exist between the systems however duplicate cases are often difficult to positively detect based upon the sometimes limited information provided. For the purposes of this report, each patient identified in any of the three systems was treated as a unique case. This allows for the most conservative evaluation of the safety data available. Limitations to each data source are discussed but the integrated summary of data from all sources strengthens the validity of the conclusions drawn.

7.6.1 Evidence in the Medical Literature

MedLine, PubMed, Excerpta Medica Database (EMBASE), International Pharmaceutical Abstracts (IPA) and Cochrane Library were searched individually in order to provide the widest search possible on pediatric exposures to both single and multiple ingredient intranasal products containing phenylephrine, oxymetazoline or xylometazoline. Searches included all years since market entry in each database. Keywords used were the drug name (phenylephrine, oxymetazoline or xylometazoline) OR the chemical abstract services number (CAS) and were limited to humans and English language when these options were available. Additional search limits were not imposed regarding route of administration or age due to the inconsistencies in the literature. Rather, these parameters were evaluated during the abstraction process outlined below.

The full text was obtained for any citation that was believed to contain safety information. Full text of the article was also obtained for citations that did not contain enough information in the title and abstract to determine if the article met the case criteria (i.e. only a title was listed and the age range studied could not be determined from the title).

Articles were systematically abstracted to evaluate inclusion for analysis. Abstraction fields included number of patients exposed, age, drug, route of exposure and presence of efficacy or

safety data. Reports were limited to those that occurred in the United States. This limitation was based on the current reporting requirements outlined in the Dietary Supplement and Nonprescription Drug Consumer Protection Act which limits reports to those that occur when the drug is used in the United States [15]. Reports were excluded if they did not report a route of exposure or reported a route of exposure other than intranasal (i.e. ocular) as these exposures were outside the scope of this analysis and introduced confounders that would have hampered an accurate safety analysis of intranasal use. Case eligibility was based upon abstracted data using the case criteria outlined below:

- Humans
- <12 years of age (including actual age, newborn, neonate, infant, toddler, child, children, adolescent, preschooler)
- Exposure to at least one of the following: phenylephrine, oxymetazoline, or xylometazoline
- Intranasal exposure
- Safety data
- Exposure occurred in the United States [based on the Dietary Supplement and Nonprescription Drug Consumer Protection Act which requires that "…any report received of a serious adverse event associated with such drug when used in the United States" be submitted [15].

Limitations of medical literature include the following:

- Safety data is not included in all articles with exposures to phenylephrine, oxymetazoline, and xylometazoline.
- Ages of the individuals with adverse events is not always reported in the articles.
- The type of exposure to phenylephrine, oxymetazoline and xylometazoline is not always reported (ex. intranasal, oral, intradermal etc.).
- Not all adverse events to phenylephrine, oxymetazoline or xylometazoline are reported and not all reported events have a published article or abstract written about them. Therefore, the medical literature will likely not include all adverse events to these ingredients.

7.6.2 Evidence in the National Poison Data System (NPDS)

The National Poison Data System (NPDS) of the American Association of Poison Control Centers (AAPCC) collects exposure information from regional poison control centers across the United States. A total of 61 regional poison centers provide coverage for the entire United

States. Exposure data is systematically collected from all centers and uploaded to NPDS, a central data repository. Standardized fields include demographic information (age, gender), reason for reporting exposure (intentional, unintentional, adverse drug reaction), exposure characteristics (acuity, route of exposure, number of substances, exposure site), medical management (health care facility level of care), clinical effects (related, unrelated) and medical outcome (level of effect).

NPDS was searched from 01 January 2000 through 30 October 2008 for human exposures to intranasal products containing phenylephrine, oxymetazoline, or xylometazoline. Both single ingredient and multiple ingredient products were included in the search criteria. The search was limited to children under the age of 12 years.

Cases were stratified by year, age group, reason for exposure, medical outcome and seriousness. Seriousness was determined using the data available in NPDS as it is not a specific field in the database. Cases were categorized as serious/fatal, serious/non-fatal, nonserious and unable/not followed by using the standardized NPDS definitions for medical outcome and health care facility level of care. A serious case was defined as any case in which the patient was admitted to an inpatient unit, had a medical outcome of major effect, or reported death. Cases with a known outcome that did not meet the serious criteria are classified as nonserious. Cases that are either not followed or in which the poison center was unable to follow are judged as unable/not followed.

This data was used to characterize the safety profile of these drugs as reported to poison centers nationwide.

Limitations of NPDS data include:

- NPDS only captures spontaneous reports, true number of exposures is unknown
- Seriousness was determined using the data available in NPDS as it is not a specific field in the database.

7.6.3 Evidence in the Adverse Event Reporting System (AERS/SRS)

Starting in 1969, FDA has collected spontaneously reported AE reports related to drugs and biologicals marketed in the United States. In succession, two databases have been used. The first was the SRS, which covered approximately 28 years from late 1969 to October 31, 1997. The SRS database consists of seven files and contains reports of 1.49 million cases involving a total of 2.79 million drugs and 2.88 million AE terms. The SRS database is now closed and is maintained for archival purposes only. The drug safety database currently in use at FDA is AERS and contains cases reported from 01 November 1997 to the present time.

A combined listing and analysis of the AE reports for the three intranasal ingredients contained in the two drug safety databases maintained by FDA was completed. The databases covered the period from January 1969, the inception of the first FDA Drug Safety database, to 31 January 2008, the date of the latest publicly available safety data at the time of this writing. The file and record structures of the two databases are different but for the purposes of this report the adverse data have been merged and will be presented together.

Using a composite list of trade names, the generic name and approximate matching techniques, the drug master file from each of the two databases (SRS and AERS) was queried for all case reports for which a phenylephrine-containing product was recorded as a suspect agent (SRS database) or the primary, secondary suspect or interacting agent (AERS database). Case reports for which phenylephrine was recorded as a concomitant medication were not included. Only case reports for which phenylephrine had a nasal, inhalation, topical or no reported route of administration were retained. Following this filtering of the data, only cases for patients less than 12 years of age were included. This process was repeated for oxymetazoline- and xylometazoline- containing products. Since the only formulation available in the US for oxymetazoline and xylometazoline is a nasal solution, all cases without explicit route of administration data were deemed topical exposures. While duplicate cases were suspected, all reports were considered unique cases for the purposes of this report. This allows for the most conservative view of safety for these products.

Limitations of AERS include:

- The publicly available data are restricted and in many cases incomplete. Duplicate records can not be purged with complete certainty from either database because the case identifying data are extremely limited and reports regarding the same case are sometimes received from several different sources at different times.
- With respect to disease information, neither database identifies the underlying diagnosis for a given patient. Since the data release for second quarter of 2002, the FDA began including information on the indication(s) for which suspect drugs have been used. However, since the data are available for only a minority of reports, they have not been tabulated for this report. In both databases, AE terms are simply listed and are neither ranked nor otherwise identified for relative importance. The AERS database, as publicly released, makes no provision for any narrative data. The SRS database has a Comment file that was seldom used.
- As far as the source of a report is concerned, more than one source from a fixed list unique to each database could be recorded. The available entries enable one to indicate whether a report is of foreign origin, but until third quarter of 2005 no information on the country of origin was provided. The primary value of the source data is to determine if a report came from a consumer or health professional. In general, source

reporting is incomplete and therefore all reports were analyzed, including those deemed foreign reports.

- Outcome data in both databases are limited to a small number of choices and, for the AERS database, none of them provides any indication of recovery status. An “Other” checkbox for the Outcome on the MedWatch form which is used to report data to the AERS database has recently been changed to indicate that its use connotes a serious outcome. For the purposes of this report, cases with only “Other” recorded as an outcome are regarded as not serious.

7.6.4 Results of Comprehensive Systematic Review Support GRASE Designation

Overall, a total of 2,408 patients met the case criteria including: 1) child less than twelve years of age; 2) exposed to phenylephrine, oxymetazoline or xylometazoline; and 3) route of exposure was topical, intranasal, inhalation. Route of administration was expanded from just intranasal to include topical and inhalation as well based upon the manner of data collection in these systems. It was often difficult to discern an intranasal exposure from a topical exposure therefore all were evaluated to be most inclusive. Ophthalmic exposures, namely to phenylephrine and cases of unknown route of exposure were excluded to focus the analysis on the safety of these drugs when used as nasal decongestants.

A little over half (1,323; 55%) of the 2,408 patients were exposed to oxymetazoline, 1,008 (42%) exposed to phenylephrine and only 77 (3%) exposed to xylometazoline (Table 7-2). Of the 2,408 patients exposed to one of the three drugs of interest, almost half (1,106; 46%) did not report any adverse events and another 1,041 (43%) cases were of unknown seriousness. Cases were judged nonserious in 217 (9%), serious (non-fatal) in 39 (2%) cases and serious (fatal) events in only five (0.2%) cases.

Table 7-2 Number of Cases by Seriousness Following Pediatric Intranasal Exposure to Phenylephrine, Oxymetazoline and Xylometazoline in Children from all Sources

Ingredient	Serious /fatal (%)	Serious/ non-fatal (%)	Nonserious (%)	Unknown Seriousness (%)	No AEs (%)	Total No. of Patients (%)
phenylephrine	4 (0.4)	10 (1.0)	72 (7.1)	479 (47.5)	443 (43.9)	**1,008 (41.9)**
oxymetazoline	0 (0.0)	17 (1.2)	141 (10.7)	543 (41.0)	622 (47.0)	**1,323 (54.9)**
xylometazoline	1 (1.3)	12 (15.6)	4 (5.2)	19 (24.7)	41 (53.2)	**77 (3.2)**
Total	**5 (0.2)**	**39 (1.6)**	**217 (9.0)**	**1041 (43.2)**	**1106 (45.9)**	**2,408 (100.0)**

The five death cases are outlined in Table 7-3. One death was reported in the medical literature and 3 reported to AERs. As mentioned, all cases were assumed unique for purposes of this report. However, it appears as though the first three case listings in the table are the same case (one report in the medical literature and two reports from AERS). Neosynephrine (0.5%) was applied to each nostril in a 4 year old boy following adenoidectomy to ensure hemostasis. The boy experienced hypertension, tachycardia, pallor, and discolored sputum. Despite resuscitation efforts he expired 16 hours after surgery. The patient had a pre-existing condition (history of heart murmur) which could have contributed to the fatal outcome.

The next case is that of a 9 year old female exposed to lidocaine, phenylephrine and saline. She experienced hypertension, pulmonary oedema and cardiac arrest following exposure for an unknown indication. Only limited information was reported for this case and many characteristics are unknown. The final fatality was a 3 year old male exposed to xylometazaline. “Death” was the only associated AE term. No additional information is available.

The low overall incidence of both serious and nonserious adverse events as well as the large percentage of cases that did not report any adverse events support the beneficial safety profile of these drugs, particularly since they have been available and widely used as OTC products for decades. While these overall numbers indicate a positive safety profile, it is important to also evaluate each drug independently. The following sections outline the results of our drug specific review for phenylephrine, oxymetazoline and xylometazoline.

Table 7-3. Death Case Summaries from all Sources

Age	Gender	Data Source	Drugs and Dose	Event Date	Indication	Medical History	Complications	SOC Terms	PT Terms
4 years*	male	medical literature	approximately 3 drops of 0.5% neosynephrine were instilled into each side of the nose	2/7/1997	to ensure hemostasis after an adenoidectomy	heart murmur	blood pressure was noted to be 180 over 110 with a heart rate of 160, the child's anesthetic agent was deepened and labetal 2.5 mg i.v. was administered, patient's color was abnormal and was white or ashen in color, patient was re-intubated, the larynx was difficult to visualize due to frothy, pink fluid, the patient became bradycardic and resuscitation efforts continued, blood levels taken approximately 1 hour following the initial dose of phenylephrine revealed phenylephrine to be present in the child's blood, indicating absorption of the administered dose, the child's blood pressure stabilized on dopamine and epinephrine drip following aggressive resuscitation efforts, the child was transferred to a tertiary care center where he died approximately 16 hours later	General Disorders and Administration Site Conditions	Death
								Investigations	Heart rate increased
								Respiratory, thoracic and mediastinal disorders	Sputum discoloured
								Vascular Disorders	Hypertension
									Pallor
4 years*	male	AERs	neo-synephrine (nasal), trandate (IV), cefazolin, fentanyl and halothane	2/7/1997	not reported	not reported	bradycardia, tachycardia, hypertension and hypotension	Cardiac Disorders	Bradycardia
									Tachycardia
								Vascular Disorders	Hypertension
									Hypotension
4 years*	male	AERs	neo-synephrine (nasal), 0.5 dose per anesthesiologist	2/7/1997	not reported	not reported	death, device failure	Injury, poisoning, and procedural complications	Device failure
9 years	female	AERs	lidocaine (nasal), normal saline, phenylephrine (route of administration not provided)	1994	not reported	not reported	cardiac arrest, pulmonary oedema, hypertension	Cardiac Disorders	Cardiac arrest
								Respiratory, thoracic and mediastinal disorders	Pulmonary oedema
								Vascular Disorders	Hypertension
3 years	male	AERs	xylometazoline, dose information was not reported, route information was not reported	July 1984	not reported	not reported	death, no other case information was provided	General Disorders and Administration Site Conditions	Death

*All of these cases appear to be identical due to event date, age and gender. This patient was reported in both the medical literature and AERs.

7.6.5 Intranasal Phenylephrine has a Positive Safety Profile in Children

Phenylephrine may be administered as an intranasal, oral, ocular or parenteral product. The multiple routes of exposure available for phenylephrine pose a challenge when characterizing the safety profile due to the diverse use of the drug. When administered intranasal as an OTC nasal decongestant, a favorable safety profile is evident as described in this section. However, when administered via a route other than intranasal (i.e. ophthalmic), for an indication other than nasal congestion or at a higher dose than the monograph indicates, the safety profile is more difficult to ascertain. The monograph designation of GRASE is based upon the use of phenylephrine as a nasal decongestant at the therapeutic doses indicated. Since this is the classification we are evaluating, only intranasal, topical or inhalation routes of phenylephrine exposure were included.

A total of 565 cases of the 1,008 cases from the literature, FDA databases and NPDS reports, reported adverse events associated with intranasal, topical or inhalation use of phenylephrine (Table 7-2). The seriousness of the event could not be determined in almost half (48%) of the cases however an equivalent amount of cases (44%) reported no adverse event at all. Almost all of the cases of unknown seriousness were NPDS reports which were not followed to a known outcome. Another 72 (7%) cases were not serious, 10 (1%) serious/non-fatal and 4 (0.4%) serious resulting in death.

A total of 626 adverse events occurred in 565 children following intranasal use of phenylephrine (Table 7-4). In some NPDS cases, the specific event was not always reported. A case may have had a medical outcome of minor, moderate or major effect but the signs, symptoms or other specific medical consequences were not indicated. For phenylephrine, 423 cases reported a medical effect but did not specify the adverse event. Of the remaining 203 events, 51 (25%) were judged serious. While the total number of cases that reported an adverse event was significantly higher than xylometzoline and similar to oxymetazoline, four of the five deaths were reported with use of this drug.

The most common events by MedDRA System Organ Class (SOC) reported following exposure to phenylephrine were classified as general disorders and administration site conditions (43 events, 2 of which were serious). Other SOCs with at least 20 events were psychiatric disorders, respiratory thoracic and mediastinal disorders, nervous system disorders, and gastrointestinal disorders.

Table 7-4. Number of Adverse Events Associated with Pediatric Intranasal Phenylephrine Exposures

Number of Adverse Events by System Organ Class and Age Group – Total Phenylephrine, All Databases

System Organ Class (SOC)	<2 Years	2 to <4 Years	4 to <6 Years	6 to <12 Years	<12 Years	Total
	No. of Events (No. of Serious Events)					
Blood and lymphatic system disorders	1(1)			1(1)		**2(2)**
Cardiac disorders	7(4)		2(2)	4(4)		**13(10)**
Congenital, familial and genetic disorders						
Eye disorders	1				3	**4**
Gastrointestinal disorders	6(1)	6(1)	3	5		**20(2)**
General disorders and administration site conditions	18(1)	6	4(1)	2	13	**43(2)**
Infections and infestations				1		**1**
Injury, poisoning and procedural complications			1(1)			**1(1)**
Investigations	1(1)		1(1)	7(7)		**9(9)**
Musculoskeletal and connective tissue disorders	1					**1**
Nervous system disorders	20(1)	2	1	2	2	**27(1)**
Pregnancy, puerperium and perinatal conditions						
Psychiatric disorders	27(1)	7	2	2(1)		**38(2)**
Renal and urinary disorders						
Respiratory, thoracic and mediastinal disorders	6(3)	1	3(1)	19(10)		**29(14)**
Skin and subcutaneous tissue disorders	3			2		***5***
Vascular disorders	1		4(4)	5(4)		**10(8)**
Subtotal of Specified Adverse Events	92(13)	22(1)	21(10)	50(27)	18	**203(51)**
Specific adverse event not reported	300 (0)	62 (0)	37 (0)	24 (0)	0 (0)	**423 (0)**
Total	**392 (13)**	**84 (1)**	**58 (10)**	**74 (27)**	**18**	**626 (51)**

Medical literature includes only adverse events with known exposures to children less than 12. There were other exposures to children less than 12 but it was not reported if the adverse events occurred in children less than 12.

The level of seriousness by term was not available by age for the AERs data and is reported for the total dataset. There were three deaths reported, representing 8 terms.

* The study authored by M. Green, 1966, grouped the subjects into an age group of 3 to 13 years.

7.6.5.1 Medical Literature Reports Support GRASE Classification for Phenylephrine

There were 48 adverse events in children less than 12 reported in the medical literature out of 23 children who reported an adverse event following exposure to phenylephrine. Another 201 children were exposed but did not experience an adverse event. Five events were reported for a single case that was serious with a fatal outcome, 25 events in 4 patients were serious with a non-fatal outcome, and 18 events in 18 children were non-serious.

- The five serious (fatal) adverse events occurred in one child. In a case report, a 4 year old male received approximately 3 drops of 0.5% neosynephrine into each side of the nose after an adenoidectomy to ensure hemostasis [16] (Table 7-4). In this case, the indication for usage was not nasal decongestion, the patient had a pre-existing condition (history of heart murmur) which could have contributed to the fatal outcome, and the reported amount of drug the patient received was inconsistent. The relationship of the death to the phenylephrine exposure was unclear.

- From two case reports and a clinical study including case reports, 25 serious and non-fatal adverse events occurred in 4 patients with co-morbidities including asthma [5], the drug was used for prolonged periods of time and amount of drug used was not clear [17], the drug was used pre- or post-operatively and for conditions different than the OTC drug products, including nasal intubation and anesthesia [18].

- The 18 non-serious adverse events occurred in 18 patients and included burning sensation, stinging sensation of eyes, watering of the eyes, and failure to tolerate treatment. In a double-blind crossover study, five adverse events were reported in patients receiving 0.25% phenylephrine hydrochloride for allergic rhinitis [19] and in a randomized double-blind placebo controlled study, 13 adverse events in patients receiving phenylephrine nose drops or spray for treatment of acute otitis media [20]. It is difficult to know how much drug was actually administered and if these adverse events occurred due to the drug or the condition itself.

Overall, children less than 12 who received phenylephrine for nasal decongestion or similar indications had non-serious adverse events, children who received phenylephrine pre- or post-operatively had more serious adverse events, and children who received an unspecified amount of phenylephrine or who received it for prolonged periods of time had more serious adverse event outcomes.

7.6.5.2 NPDS Data Support GRASE Classification for Phenylephrine

Overall, 3,161 cases of exposure with phenylephrine intranasal products were reported for children under the age of twelve years. While the search was restricted to intranasal formulations only, the reported routes of exposure included inhalation/intranasal (as the

combined code used in NPDS) as well as oral and ocular exposures. Most often the non-inhalation/intranasal cases associated with phenylephrine intranasal products were the result of an unsupervised or accidental exposure in young children. In 2000, the total number of exposures to children under the age of twelve years was 204 cases. This number increased steadily peaking in 2006 with 453 cases. After 2006, the number of exposures reported to NPDS declined with 396 cases reported in 2007 and 257 cases reported in the first three quarters of 2008. Almost two-thirds of all phenylephrine cases (60%) were reported in children age two years or less. The remaining cases occurred in: children age two to less than four years reported, 30%, age four to less than six years, 7%, and age six to less than twelve years, 4%.

There were no deaths reported to NPDS. Of the 3,161 cases associated with exposures to phenylephrine intranasal products, 1,336 were able to be followed to a known outcome. Of the 1,336 cases, 11 were classified as serious (nonfatal). Nine of these 11 cases occurred in children age less than two years. The remaining two cases occurred in one child age two to less than four years and one child age four to less then six years. Of the nine serious (nonfatal) cases occurring in children age less than two years the medical outcome was a major effect in one case and either a moderate or no/unrelated effect in the remaining eight cases. All serious (nonfatal) exposures occurred at the child's own residence and were unintentional. Nine of the serious (nonfatal) cases reported a single substance exposure. There were 1,325 nonserious cases reported. Of these cases, 792 (60%) occurred in children under the age of two years, 407 (31%) occurred in children age two to less than four years, 84 (6%) occurred in children age four to less than six years and 40 (3%) in children age six to less than twelve years.

Overall, 773 cases reported to NPDS were inhalation/nasal phenylephrine exposures. Of the 773 inhalation/nasal phenylephrine exposures 296 were able to be followed to a known outcome. There were no deaths or serious (fatal) events reported. Of these 296 cases, three were reported as serious. All three serious (nonfatal) cases were reported in children age two years or less. These cases could be followed to a known outcome with one case reporting a major effect, one reporting a moderate effect and one reporting no/unrelated effect. All three serious (nonfatal) cases occurred at the child's own residence and two of the cases reported a single substance exposure.

The serious (nonfatal) events with greater than a minor effect have all been reported in children under the age of two years. There were no deaths or serious (fatal) exposures of inhalation/nasal phenylephrine.

7.6.5.3 AERS Reports Support GRASE Classification for Phenylephrine

An analysis of the AEs reported for topical phenylephrine from the FDA's SRS and AERS databases identified 30 pediatric cases (ages < 12 years) involving 82 AE terms. A review of the actual case listings revealed that 10 cases had possible duplicate (or in one case triplicate)

entries in the database and one of these duplicated cases was a death. It is likely the databases have only 19 unique pediatric cases of topical exposure to phenylephrine of which two are reports of deaths. However, since the 11 possible duplicates could not be purged with absolute certainty, for completeness they have been retained in the dataset analyzed for this report.

The 30 pediatric cases represented 9.1% (30/329) of all cases for topical phenylephrine in the FDA databases. Among the pediatric reports for phenylephrine, there were 13 serious cases (43.3%, 13/30) with 39 associated AE terms and 3 reports of deaths (10.0%, 3/30) with 8 associated terms. Four cases (13.3%, 4/30) had no reported outcome. The AERS database contributed 33.3% (10/30) of the reports and the SRS database contributed 66.7% (20/30). Females represented 50.0% (15/30) of the total reports and males accounted for 50.0% (15/30).

Overall, four SOCs accounted for 61.0% (50/82) of all the reported terms. These were: Cardiac disorders (22.0%, 18/82), Investigations (14.6%, 12/82), Gastrointestinal disorders (12.2%, 10/82) and Respiratory, thoracic and mediastinal disorders (12.2%, 10/82).

In general, the terms are broadly distributed and only 8 terms have more than two occurrences. Thirty-nine of the 82 terms were reported for serious cases; 18 were for non-serious cases; 8 terms were reported for the 3 deaths and 17 terms were for cases without outcome data. Bradycardia was the most frequently reported term with 8 occurrences (9.8%, 8/82). Hypertension (7.3%, 6/82), pulmonary oedema (6.1%, 5/82), cyanosis (4.9%, 4/82) and tachycardia (4.9%, 4/82) were the next most frequently reported terms.

For serious reports, there were 13 cases with 39 associated AE terms and three SOCs accounted for 59.0% (23/39) of all the reported terms. These were: Investigations (25.6%, 10/39), Cardiology disorders (17.9%, 7/39) and gastrointestinal disorders (15.4%, 6/39). The individual AE terms for the serious reports were distributed across a wide range of events and the absolute reporting rates were, in general, low. No individual term in any age range had more than 3 reports. The three most frequently reported terms were bradycardia, pulmonary oedema and hypertension each with 3 reported terms (7.7%, 3/39).

There were 3 reported deaths with 8 associated AE terms. Only Hypertension (25.0%, 2/8) had more than a single occurrence.

When stratified by route of administration, the majority of cases and reported terms were ophthalmic, where there were 19 cases (63.3%, 19/30) and 57 associated AE terms (69.5%, 57/82). In the ophthalmic group, 14 terms were in the cardiac disorders SOC (24.6%, 14/57), 12 terms were in the Investigations SOC (21.1%, 12/57) and 7 were in the gastrointestinal disorders (12.3%, 7/57). Bradycardia (12.3%, 7/57) and cyanosis (7.0%, 4/57) were the two most commonly reported terms in the ophthalmic route of administration. The nasal route of administration had 6 reports with 13 associated AE terms. Only hypertension (three instances) and pulmonary oedema (two instances) had more than single reports of any individual AE term.

When stratified by age, the majority of cases and reported terms were in the < 2 year age range, where there were 20 cases (66.7%, 20/30) and 60 associated AE terms (73.2%, 60/82). In the < 2 year age range, 14 terms were in the cardiac disorders SOC (23.3%, 14/60), 12 terms were in the Investigations SOC (20.0%, 12/60) and 9 were in the gastrointestinal disorders (15.0%, 9/60). Bradycardia (11.7%, 7/60) and cyanosis (6.7%, 4/60) were the two most commonly reported terms in the < 2 year age range.

With respect to the gender differences, although the absolute frequencies are small, all 5 reports of pulmonary oedema and 5 of the 6 reports of hypertension were in females. Considered overall, no statistically reliable gender-dependent clustering of AEs was noted.

Overall, for the pediatric data available from the FDA databases for phenylephrine, the majority of cases and AE terms were reported in the < 2 year age range. With regard to route of administration, of the 19 ophthalmic reports 9 were categorized as serious, whereas for the 6 nasal reports 2 were serious and 2 were deaths (1 of the deaths was probably a duplicate report). The AEs reported were broadly distributed with 38 of the 82 AE terms reported in the cardiac disorders, gastrointestinal disorders or respiratory, thoracic and mediastinal disorders SOCs. There were 3 deaths; 2 in the 4 to < 6 year age range (1 of these was probably a duplicate) and 1 in the 6 to < 12 age range.

7.6.6 Intranasal Oxymetazoline has a Positive Safety Profile in Children

A total of 1,323 (55%) cases from the literature, FDA databases and NPDS reports involved an intranasal exposure to oxymetazoline (Table 7-2). The patient did not experience an adverse event in the majority (622; 47%) of cases with another 543 (41%) experiencing an event of unknown seriousness. As mentioned, almost all of these cases were NPDS reports which were not followed to a known outcome. Another 141 (11%) cases were not serious and 17 (1%) serious (non-fatal). No reported intranasal oxymetazoline exposures resulted in death.

A total 785 adverse events occurred in 701 children following intranasal use of oxymetazoline (Table 7-5). In some NPDS cases, the specific event was not always reported. A case may have had a medical outcome of minor, moderate or major effect but the signs, symptoms or other specific medical consequences were not indicated. For oxymetazoline, 443 cases reported a medical effect but did not specify the adverse event. Of the remaining 342 events, 36 (11%) were judged serious. While the total number of cases was greater than the other two drugs studied, the events tended to be less serious and no deaths were reported.

The most common events by MedDRA SOC reported following exposure to oxymetazoline were classified as respiratory thoracic and mediastinal disorders (69 events, 7 of which were serious). Other SOCs with at least 60 events were nervous system disorders, gastrointestinal disorders and general disorders and administration site conditions.

Table 7-5. Number of Adverse Events Associated with Pediatric Intranasal Oxymetazoline Exposures

Number of Adverse Events by System Organ Class and Age Group - Oxymetazoline, Total All Data Sources						
System Organ Class (SOC)	**<2 Years**	**2 to <4 Years**	**4 to <6 Years**	**6 to <12 Years**	**<12 Years**	**Total**
	Total No. of Events (No. of Serious Events)					
Blood and lymphatic system disorders						
Cardiac disorders	5 (5)	1 (1)	1	6 (1)	1	**14 (7)**
Congenital, familial and genetic disorders		1 (1)	1			**2 (1)**
Eye disorders	2	4 (1)	1	3		**10 (1)**
Gastrointestinal disorders	36	4 (1)	6	19		**65 (1)**
General disorders and administration site conditions	24 (3)	11 (2)	12	18		**65(5)**
Infections and infestations	2 (2)					**2 (2)**
Injury, poisoning and procedural complications						
Investigations						
Musculoskeletal and connective tissue disorders						
Nervous system disorders	31 (3)	11	6	18 (1)		**66 (4)**
Pregnancy, puerperium and perinatal conditions						
Psychiatric disorders	11	4	5	4		**24**
Renal and urinary disorders						
Respiratory, thoracic and mediastinal disorders	17 (6)	5	6	41 (1)		**69 (7)**
Skin and subcutaneous tissue disorders	1	9 (5)	5	4		***19 (5)***
Vascular disorders	3 (2)	1 (1)	1	1		**6 (3)**
Subtotal of Specified Adverse Events	132 (21)	51 (12)	44	114 (3)	1	**342 (36)**
Specific adverse event not reported	192 (0)	89 (0)	55 (0)	105 (0)	2 (0)	**443 (0)**
Total	**324 (21)**	**140 (12)**	**99 (0)**	**219 (3)**	**3 (0)**	**785 (36)**

Medical literature includes only adverse events with known exposures to children less than 12. There were other exposures to children less than 12 but it was not reported if the adverse events occurred in children less than 12.

7.6.6.1 Medical Literature Reports Support GRASE Classification for Oxymetazoline

There were four adverse events that occurred in 79 children following exposure to oxymetazoline reported in the medical literature. Three of these adverse events were serious and non-fatal and one was non-serious.

- The three serious and non-fatal adverse events occurred in a 1 day old who received various doses of phenylephrine and oxymetazoline over a period of several weeks. It is unclear if these adverse events (tachyphylaxis, peripheral cyanosis, and 45 to 50 second episode of apnea) occurred due to exposure to phenylephrine or oxymetazoline [17]. It is also unclear the exact amount this patient received.

- Reported in a case report, the one adverse event that was non-serious (burning sensation) occurred in a 9 year old who received oxymetazoline hydrochloride for allergic rhinitis [19].

Overall, there were very few adverse events to oxymetazoline reported in the medical literature in children less than 12 years. The patient that experienced serious and non-fatal adverse events was an infant who received various doses of both phenylephrine and oxymetazoline.

7.6.6.2 NPDS Data Support GRASE Classification for Oxymetazoline

Overall, 5,722 cases of exposure with oxymetazoline intranasal products were reported for children under the age of twelve years. A subset of cases (1,231; 22%) reported to NPDS were intranasal routes of exposure to oxymetazoline and are included in this report. Results of these analyses were similar to that of all oxymetazoline exposures.

Of the 1,231 intranasal oxymetazoline exposures 690 were followed to a known outcome. There were no deaths reported. Of these 690 cases, 15 were reported as serious; 12 were reported in children age two years or less, two were reported in children age two to less than four years, and one was reported in a child age six to less than twelve years. All of these cases were followed to a known outcome: six cases with a moderate effect, two cases with a minor effect and seven cases with no or unrelated effect. Fourteen of the serious (nonfatal) cases occurred at the child's own residence and were unintentional exposures. All 15 serious (nonfatal) cases reported a single substance exposure.

The majority (80%) of serious (nonfatal) events have all been reported in children under the age of two years. There were no deaths associated intranasal oxymetazoline exposures.

7.6.6.3 AERS Reports Support GRASE Classification for Oxymetazoline

An analysis of the AEs reported for topical oxymetazoline from the FDA's SRS and AERS databases covering the period from 1969 to 31 March 2008 identified 15 cases involving 31 AE

terms for pediatric patients < 12 years old. This represented 3.0% (15/505) of all cases for oxymetazoline in the FDA databases as of 31 March 2008. Among the pediatric reports for oxymetazoline, there were 9 serious cases (60.0%, 9/15) with 23 associated AE terms. There were no reports of death. Two cases (13.3%, 2/15) had no reported outcome. The AERS database contributed 26.7% (4/15) of the reports and the SRS database contributed 73.3% (11/15). Females represented 33.3% (5/15) of the total reports, males accounted for 40.0% (6/15) and 26.7% (4/15) of the cases had no reported gender.

Overall, four SOCs accounted for 54.8% (17/31) of all the reported terms. These were: Cardiac disorders (16.1%, 5/31), General disorders and administration site conditions (12.9%, 4/31), Nervous system disorders (12.9%, 4/31) and Skin and subcutaneous tissue disorders (12.9%, 4/31).

In general, the AE terms are broadly distributed and only 9 terms have more than a single occurrence and each of these 9 has 2 reports. Twenty-three of 31 terms were reported for serious cases; 5 were for non-serious cases; and 3 were for cases without outcome data. Two of the 15 pediatric cases (1 Not serious, 1 Serious) involved accidental oral ingestion of Afrin (1 case) or Visine (1 case).

For serious reports, there were 9 cases with 23 associated AE terms. Two of the cases were in the < 2 year age range, 5 were in the 2 - <4 age range and 2 cases were in the 6 - <12 year age range. Three SOCs accounted for 52.2% (12/23) of all the reported terms. These were: Cardiac disorders (17.4%, 4/23), General disorders and administration site conditions (17.4%, 4/23) and Skin and subcutaneous tissue disorders (17.3%, 4/23). The individual AE terms for the serious reports were distributed across a wide range of events and the absolute reporting rates were, in general, low. No individual term in any age range had more than 2 reports. The five most frequently reported terms were cyanosis (8.7%, 2/23), Drug tolerance increased (8.7%, 2/23), rhinitis (8.7%, 2/23), apnoea (8.7%, 2/23) and Stevens-Johnson syndrome (8.7%, 2/23).

There were no reported deaths.

When stratified by age, the largest fraction of cases and reported terms were in the 2 to < 4 year age range, where there were 7 cases (46.7%, 7/15) and 15 associated AE terms (48.4%, 15/31). No other pediatric age range had more than 3 cases. Seven of the 15 terms in the 2 to < 4 year age range were in two SOCs. Skin and subcutaneous tissue disorders had 4 terms and Nervous system disorders had 3 terms. In this age range, the two most frequently reported AE terms were somnolence (13.3%, 2/15) and Stevens-Johnson syndrome (13.3%, 2/15).

With respect to the gender differences in the overall distribution of AEs, no apparent clustering by SOC or AE term was observed in the data. In general, there were too few terms to permit meaningful comparisons between genders.

Overall, there were few cases in the FDA databases for pediatric cases associated with oxymetazoline. Almost half of cases and AE terms were reported in the 2 to < 4 year age range and the two reported cases of Stevens-Johnson syndrome were in this age range. The side effects were distributed over a broad range of AEs. There were no deaths reported. Considered overall, there was no consistent clinically important gender-dependent clustering of AEs.

7.6.7 Intranasal Xylometazoline has a Positive Safety Profile in Children

Over half (53%) of patients exposed to intranasal xylometazoline did not experience an adverse event (Table 7-2). Four (5%) were nonserious, 12 (16%) were serious (non-fatal) and one case (1%) was serious (fatal). Nineteen (25%) cases were of unknown seriousness. As mentioned, almost all of these cases were NPDS reports which were not followed to a known outcome.

A total of 70 adverse events occurred in 36 children following intranasal use of xylometazoline (Table 7-6). In some NPDS cases, the specific event was not always reported. A case may have had a medical outcome of minor, moderate or major effect but the signs, symptoms or other specific medical consequences were not indicated. For oxymetazoline, 12 cases reported a medical effect but did not specify the adverse event. Of the remaining 58 events, 41 (71%) were judged serious. While the total number of cases was significantly lower than the other two drugs studied, the events were more often serious with one resulting in death.

The most common events by MedDRA SOC reported following exposure to xylometazoline were classified as nervous system disorders (18 events, 12 of which were serious). Other SOCs with at least five events were cardiac disorders, general disorders and administration site conditions, injury poisoning and procedural complications, psychiatric disorders, and respiratory thoracic and mediastinal disorders.

Table 7-6. Number of Adverse Events Associated with Pediatric Intranasal Xylometazoline Exposures

Number of Adverse Events by System Organ Class and Age Group - Xylometazoline, Total All Databases						
System Organ Class (SOC)	**<2 Years**	**2 to <4 Years**	**4 to <6 Years**	**6 to <12 Years**	**<12 Years**	**Total**
	No. of Events (No. of Serious Events)					
Cardiac disorders	4 (3)			1 (1)		**5 (4)**
Eye disorders	1 (1)					**1 (1)**
General disorders and administration site conditions	4 (2)	1 (1)	1	1 (1)		**7 (4)**
Hepatobiliary disorders	1 (1)					**1 (1)**
Injury, poisoning and procedural complications	5 (3)					**5 (3)**
Investigations	2 (2)					**2 (2)**
Metabolism and nutrition disorders	1 (1)					**1 (1)**
Musculoskeletal and connective tissue disorders	1					**1**
Nervous system disorders	15 (12)			3		**18 (12)**
Psychiatric disorders	4 (3)			2 (1)		**6 (4)**
Respiratory, thoracic and mediastinal disorders	5 (5)		1			**6 (5)**
Skin and subcutaneous tissue disorders			1 (1)			**1 (1)**
Surgical and medical procedures	2 (1)					**2 (1)**
Vascular disorders	1 (1)			1 (1)		**2 (2)**
Subtotal of Specified Adverse Events	46 (35)	1 (1)	3 (1)	8 (4)		**58 (41)**
Specific adverse event not reported	5 (0)	2 (0)	3 (0)	2 (0)	0 (0)	**12(0)**
Total	**51 (35)**	**3 (1)**	**6 (1)**	**10 (4)**	**0 (0)**	**70 (41)**

There were 3 cases reported as "no data" under route of administration in the AERs report. These cases are not included in the above table.

In the AERs data the route of administration was not specified for seven of the cases. However "nasal" was referred to elsewhere in the data so these cases were included in the table.

In the AERs data there was one death reported with no route of administration specified. This case was included in the "no data" category under route of administration in the AERs report, but was included in the above table.

7.6.7.1 Medical Literature Reports Support GRASE Classification of Xylometazoline

There were three adverse events that occurred in one child reported in the medical literature out of 23 children less than 12 who were exposed to xylometazoline. All three adverse events were serious and non-fatal and occurred in a one month old [21]. The patient's mother instilled one-half dropper full of xylometazoline nose drops into each nostril of the infant on three occasions in 16 hours. The authors indicated that this total dosage was three times the recommended dose for adults. No other adverse events were reported in the medical literature that included xylometazoline exposures to children less than 12 years.

7.6.7.2 NPDS Data Support GRASE Classification of Xylometazoline

There were 149 total cases of exposure with xylometazoline intranasal products reported for children under the age of twelve years. A subset of cases (38; 26%) reported to NPDS were intranasal routes of exposure to xylometazoline and are included in this report. Results of these analyses were similar to that of all xylometazoline exposures.

The largest number of cases occurred in 2001 with 13 cases and has since declined with 1 case reported each year since 2006. Also decreasing is the percentage of reported exposures to children under age two years. At the peak in 2006, 42% of all intranasal exposures were reported in children under the age of two.

Of the 38 intranasal xylometazoline exposures 22 were followed to a known outcome. There were no deaths events reported. Of these 22 cases, one was reported as serious (nonfatal). This serious (nonfatal) case was reported in a female child less than two years of age. This case was an adverse exposure at an unknown location with a single substance and reported a minor effect medical outcome.

Xylometazoline intranasal products were the least common reported drug of the nasal decongestants studied. The low exposure volume xylometazoline reported to NPDS as well as the rarity of serious events provides supporting evidence for the current GRASE classification. The positive safety profile illustrated with NPDS data is the profile expected for drugs with low systemic exposure.

One serious (nonfatal) event with a minor effect was reported in a child under the age of two years. There were no deaths associated with intranasal xylometazoline exposures.

7.6.7.3 AERS Reports Support GRASE Classification of Xylometazoline

An analysis of the AEs reported for topical xylometazoline from FDA's SRS and AERS databases identified 19 pediatric cases involving 52 AE terms. This represented 15.6% (19/122) of all cases for topical xylometazoline in the FDA databases. Among the pediatric reports for xylometazoline, there were 11 serious cases (57.9%, 11/19) with 40 associated AE terms and 1 report of a death (5.3%, 1/19) with 1 associated term. Two cases (10.5%, 2/19)

had no reported outcome. The AERS database contributed 63.2% (12/19) of the reports and the SRS database contributed 36.8% (7/19). Females represented 52.6% (10/19) of the total reports, males accounted for 36.8% (7/19) and 10.5% (2/19) of the cases had no reported gender. A total of 78.9% (15/19) reports were from foreign sources.

Overall, two SOCs accounted for 40.4% (21/52) of all the reported terms. These were: Nervous system disorders (23.1%, 12/52) and Psychiatric disorders (17.3%, 9/52).

In general, the AE terms are broadly distributed and only 6 terms have more than a single occurrence. Forty of 52 terms were reported for serious cases; 7 were for non-serious cases; 1 term was for the death and 4 were for cases without outcome data. Somnolence was the most frequently reported term with 4 occurrences (7.7%, 4/52). Apnoea and Cyanosis had 3 instances each (5.8%, 3/52).

Five reports with 20 associated AE terms (1 case had 9 terms) involved accidental or incorrect dosing. One of the reports was not serious, 3 were serious and 1 could not be categorized by seriousness. All of these cases were in the < 2 year age range. No specific dosing information was available for these cases.

For serious reports, there were 11 cases with 40 associated AE terms and six SOCs accounted for 75.0% (30/40) of all the reported terms. These were: Nervous system disorders (25.0%, 10/40), Cardiology disorders (10.0%, 4/40), General disorders and administration site conditions (10.0%, 4/40), Psychiatric disorders (10.0%, 4/40), Respiratory, thoracic and mediastinal disorders (10.0%, 4/40), and Skin and subcutaneous tissue disorders (10.0%, 4/40). The individual AE terms for the serious reports were distributed across a wide range of events and the absolute reporting rates were, in general, low. No individual term in any age range had more than 3 reports. The two most frequently reported terms were Cyanosis (7.5%, 3/40) and Apnoea (7.5%, 3/40).

There was 1 reported death in a 3 year old male in July 1984. “Death” was the only associated AE term. No dose or other case information was provided.

When stratified by age, the majority of cases and reported terms were in the < 2 year age range, where there were 12 cases (63.2%, 12/19) and 38 associated AE terms (73.1%, 38/52). No other pediatric age range had more than 3 cases. Twelve of the 38 terms in the < 2 year age range were in the Nervous system disorders SOC. The three most frequently reported terms were Somnolence (10.5%, 4/38), Cyanosis (7.9%, 3/38) and Apnoea (7.9%, 3/38). Eight of 11 (73%) serious cases were in a age group less than 2, none in a age group 2 to 4 years and only 2 serious cases in the age group 6 to 12 years.

With respect to the gender differences in the overall distribution of AEs, no apparent clustering by SOC or AE term was observed in the data.

Overall, for the pediatric data available from the FDA databases for xylometazoline, the majority of cases and AE terms were reported in the < 2 year age range and 5 of the 12 cases in this range involved medication errors or overdoses. The side effect profile observed generally appeared to involve central nervous system effects (18 of the 52 reported terms), allergic phenomena (7 of the 52 reported terms) or accidental ingestion or incorrect drug administration (5 of the 52 reported terms). There was one death in a 3 year old male reported and no additional information available.

7.6.8 Selected Safety Topics Identified From Comprehensive Safety Evaluation

An area of possible concern associated with prolonged intranasal use of these vasoconstrictor agents, is the potential for induction of rebound nasal congestion (rhinitis medicamentosea) and current recommendations are for short-term use. Although some studies demonstrate that rebound congestion does not develop with up to 8 weeks of topical decongestant use [22,23], others suggest that rhinitis medicamentosa may start within 3 to 10 days [24,25]. The inclusion in nasal spray formulations of benzalkonium chloride was shown to potentiate this effect [24]. However, there was not a single case reported of rebound congestion during the short treatment periods in any of the published clinical trials with these intranasal decongestants.

Rebound congestion and drug dependence have been reported as important safety considerations for intranasal use of phenylephrine, oxymetazoline and xylometazoline. In the FDA Federal Register (Vol. 59, No. 162), the agency's conclusions of the comments include a statement indicating that 'the agency has reviewed adverse drug reaction reports for the years 1976 to 1993 and finds that the two most frequently reported adverse events of marketed OTC topical nasal decongestant drug products are rebound congestion and drug dependence. In response to this data, the FDA now requires an expanded warning on the label and in the drug monograph to state 'Do not use this product for more than 3 days. Use only as directed. Frequent or prolonged use may cause nasal congestion to recur or worsen. If symptoms persist, consult a doctor'. These effects have not been reported in children less than twelve years of age, most likely because the drugs are administrated by a caregiver, rather than self-administered, decreasing the likelihood of excessive use, in turn avoiding rebound congestion and dependence.

Phenylephrine used for indications other than nasal congestion result in more serious adverse events than exposures intended to treat congestion. It is not uncommon for monograph drugs like phenylephrine to be used for many indications, both label and off-label. The deaths associated with phenylephrine were all related with the use of phenylephrine for an indication other than nasal congestion. It is important to understand the safety of this drug in the context of the current monograph.

7.6.9 Poison Center Management Guidelines for Pediatric Intranasal Product Exposures Provides Evidence of a Favorable Safety Profile

The Rocky Mountain Poison and Drug Center (RMPDC) is one of 61 United States regional poison centers that provide case management for both pharmaceutical and nonpharmaceutical substance exposures. Poison centers often develop substance specific management guidelines based upon experience with the substance. These guidelines include threshold doses of exposures in children that would result in a referral to a health care facility for evaluation or treatment. Since toxic doses of most substances are not studied prospectively, these guidelines are developed by studying exposure characteristics and outcomes as reported to NPDS.

At RMPDC, the threshold dose for a pediatric ingestion of phenylephrine that would result in a referral to the emergency department is more than 4 mg/kg. For example, if a therapeutic dose of phenylephrine for a 2 year old child that weighs 10 kg is 2.5 mg and the threshold dose is 40 mg, the oral exposure would have to be a 15-fold dose before the poison center would refer the child to a health care facility for evaluation. It is highly unlikely that an exposure of this magnitude would result from an intranasal product due to the smaller dose and the packaging of intranasal drugs. There are currently no threshold doses established for an intranasal exposure.

For exposures to any oxymetazoline- or xylometazoline-containing products, children less than twelve years of age would be referred to an emergency department following an ingestion of more than 7.5 mL of a 0.05% solution. This equates to half a bottle of most products on the shelf. Access to this amount of drug would be difficult for any patient due to the metered dose and other delivery mechanisms of the products. There are currently no threshold doses established for an intranasal exposure.

7.7 Discussion

In response to FDA Question 7, the data presented indicate that monographs for topical and intranasal ingredients should not be considered in a similar fashion to the oral cough and cold products. Topically administered cough and cold products offer an alternative delivery system direct to the symptomatic organ in significantly lower doses and demonstrate a lower systemic exposure to the active ingredient than that of orally administered products.

Another example of the disparity between oral and intranasal administration of the same active ingredients is in corticosteroids. Recent studies of bioavailability of these drugs indicate that a fraction of the dose is delivered with intranasal application than with oral administration of the same active ingredient. Efficacy is still achieved with the lower dose as well as a more favorable safety profile. The adverse events reported with oral use of corticosteroids are drastically minimized with intranasal administration.

During the OTC review process, topical nasal decongestants including phenylephrine, oxymetazoline and xylometazoline were judged to be GRASE. The final monograph was approved 14 years ago. Since then, the safety profile of these drugs illustrated in the medical literature, NPDS and AERS has been favorable. Adverse events, particularly serious adverse events, are rare and even unintentional exposures, including overdoses, do not typically result in clinically significant events. In regards to the management of unintentional exposures of these drugs by RMPDC, the guidelines require an oral phenylephrine ingestion of at least 15 times the oral therapeutic dose or consumption of about half a bottle of oxymetazoline or xylometazoline spray before sending the child to a health care facility for evaluation. These guidelines illustrate the relative safety of these drugs assumed by RMPDC based upon years of overdose management experience.

The limitation of spontaneous adverse event report systems is that the true number of exposures and adverse events is unknown. Additional adverse events, both serious and nonserious, have most likely occurred and gone unreported. We have attempted to account for this reporting bias by integrating multiple data sources with distinct methods, detection and adverse event collection systems.

Overall, the number of events, both serious and nonserious, is very low and supports the favorable safety and GRASE designation of these drugs considering the decades of product use. The actual number of exposures (or doses administered) may be unknown but the relatively low number of events over the long period of time which the products have been available indicates that events are not frequent and use in children less than twelve years of age is safe. The intranasal decongestants phenylephrine, oxymetazoline, and xylometazoline, when used as directed are safe and effective in children.

7.8 Summary

Topical and intranasal ingredients should not be considered in a similar manner to orally ingested cough/cold ingredients. The GRASE classification of intranasal products that contain phenylephrine, oxymetazoline or xylometazoline to treat the symptoms of nasal congestion is supported by the current analysis of available safety data obtained from multiple data sources. The favorable safety profile illustrated for these drugs is consistent with the profile expected for drugs with low systemic exposure and remains similar overall to the favorable safety profile that was considered when defining the OTC monograph status for these ingredients.

7.9 Reference List for Question 7

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Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 8

FDA Question:

"The CCABADP monograph allows for the combination of ingredients to treat colds and/or coughs. Should combination products be permitted for all pediatric age groups? Should data be provided to support each unique combination?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 8

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8 FDA QUESTION 8

"The CCABADP monograph allows for the combination of ingredients to treat colds and/or coughs. Should combination products be permitted for all pediatric age groups? Should data be provided to support each unique combination?"

8.1 Position of the CHPA Pediatric Task Force

The CHPA Pediatric Task Force maintains that combinations of pediatric cough and cold ingredients should remain available for children ages 4 years and older because they address the need for treatment of simultaneous cold symptoms and have the potential of reducing medication errors. The position of the Task Force is supported by the following:

- For the symptomatic relief of the common cold in children, it is rational to continue to provide for OTC use of combination-ingredient cough and cold products as an appropriate treatment option.
    - Children commonly develop acute respiratory tract infections (colds) with one or more symptoms including nasal congestion, cough, runny nose, pain, and fever.
    - The availability of both single- and combination-ingredient products provides the benefit of allowing parents and caregivers to tailor treatment to their child's specific cold symptoms.
    - The use of combination products reduces the likelihood of dosing errors since parents administer one product, instead of several products, to their child for relief of all of their symptoms.
    - Single ingredient and combination-ingredient pediatric cough and cold products have similar safety profiles with a very rare occurrence of serious adverse events.
- Caregivers and healthcare providers currently use both single-ingredient and combination-ingredient cough and cold products when treating children with colds when one or more symptoms are present.
    - Pediatricians recommend both single-ingredient and combination-ingredient cough and cold medicines for children less than 12 years of age.
    - Parents appropriately use both single-ingredient and combination-ingredient OTC cough and cold medications.

- It is unnecessary to confirm efficacy and safety of every combination cough and cold product when scientific data are available for the individual cough and cold ingredients consistent with FDA's OTC combination drug policy.
    - As a general principle of FDA's OTC combination policy, when effectiveness and safety data are available for individual ingredients, additional study of the combination of ingredients is not needed to confirm efficacy and safety.
    - Since OTC monograph combination medicines have a long history of safe use at therapeutic doses, unless there is a specific scientific concern for a given combination, additional safety studies are not needed.
    - Research in children should be performed only when necessary to answer new and relevant scientific questions.

8.2 OTC Combination Cough and Cold Products are a Rational Treatment Option for the Symptomatic Relief of the Common Cold

For the symptomatic relief of the common cold in children, it is rational to continue to provide for OTC use of combination-ingredient cough and cold products as an appropriate treatment option.

8.2.1 Multiple Symptoms of Common Cold in Children

Children commonly develop acute respiratory tract infections (colds) with 1 or more symptoms including nasal congestion, cough, runny nose (rhinorrhea), pain, and fever. The majority of children experience multiple symptoms concurrently. Use of multiple-ingredient medicines to treat these symptoms in children has been reported to range from 64% to 70% [9,10,16]. The percentage of older children (10 years and older) with 4 or more symptoms treatable with medicines containing ingredients in each of the following 4 categories (antitussive, antihistamine, decongestant, analgesic) has been reported to range from 45% to 57% [12,13]. In addition, the percentage of children (all ages) with symptoms treatable with medicines containing ingredients in 3 of the 4 categories has been reported to range from 16% to 56% [9,12,13]. Cough was the most frequently reported symptom in children regardless of whether it was reported alone or in combination with other symptoms [15].

Section 8.2.1.1 summarizes information from the published literature concerning the specific symptoms and combinations of symptoms that are experienced by children with colds. Section 8.2.1.2 summarizes information from unpublished reports concerning the specific symptoms and combinations of symptoms that are experienced by children with colds. Table 8-1 provides a summary of the symptoms experienced and the medications used by children with colds that are discussed in detail in Sections 8.2.1.1 and 8.2.1.2.

Children with colds experience a variety of symptoms and combinations of symptoms. Caregivers of children administer both single- and combination-ingredient products to treat the specific symptoms and combinations of symptoms that are experienced.

Table 8-1. Summary of the Symptoms Experienced and Medications Used by Children With Colds From Published and Unpublished Sources

Reference	Number of Children (Age)	Symptoms Experienced and/or Medications Used
Pappas 2008 [4]	81 (5-12 y)	At their peak: nasal congestion (88%), runny nose (72%), cough (69%), sneezing (55%), headache (20%), feverishness (15%).
Hay 2005 [6]	13,617 (0-57 mo)	Children experiencing cough: <6 mo (65%), 6 to 17 mo (84%), 18 to 29 mo (86%), 30 to 41 mo (88%), 42 to 56 mo (92%).
Kurugol 2007 [7]	120 (1-10 y)	Nasal drainage (94.2%), cough (89.2%), sore throat (69.2%), nasal congestion (61.7%), scratchy throat (55.8%), fever (52.5%), sneezing (48.3%), hoarseness (39.2%), headache (19.2%), muscle ache (18.3%).
Butler 2002 [8]	290 (1-12 y)	Coryza (80%), cough (79%), increased temperature (54%), pharyngitis (49%), enlarged lymph nodes (46%), malaise (45%).
Vernacchio 2008 [9]	439 (0-17 y)	Of the 489 products used, 35.8% were single-ingredient and 64.2% were multiple-ingredient. Multiple-ingredient products most commonly used were decongestant/first-generation antihistamine combinations (15.5%) and antitussive/decongestant/first-generation antihistamine combinations (10.4%). 16% of the cough and cold combination products used contained ingredients in 3 of the following 4 categories (antitussive, antihistamine, decongestant, analgesic). The reason given for use of the 489 products was cough (23.7%), cold (21.7%), allergy (19.6%), and not related to cough, cold, or allergy or unclear (35.0%).
Slone Epidemiology Center 2007 [10]	2857 (0-11 y)	93.7% used a cough/cold medication, of which 64.1% was a multiple-ingredient product. For children <2 y, antihistamine, antitussive, and expectorant use were most common in those 12-23 mo, and decongestant use was highest in those 6-11 mo. Use of any of the cough/cold medications in infants <6 mo (6.2%), 6-11 mo (16%), 12-23 mo (12%).
Vicks Research Center 1983 [11]	3166 (2-12 y)	<u>Assessments by mothers</u> Symptoms commonly reported: any cough (60.2%), fever (56.4%), runny nose (42.2%), sore throat (34.4%), earache (32.8%). Most frequent combinations: cough with fever (33.6%), cough with runny nose (30.5%). <u>Assessments by physicians</u> Clinical findings commonly reported: any cough (48.5%), nasal congestion (47.7%), pharyngitis (46.7%), fever (44.2%), rhinorrhea (43.3%). Most frequent combinations: cough with nasal congestion (28.9%), cough with rhinorrhea (27.3%).

Table 8-1. Summary of the Symptoms Experienced and Medications Used by Children With Colds From Published and Unpublished Sources, continued

Reference	Number of Children (Age)	Symptoms Experienced and/or Medications Used
Bristol Myers Products 1979 [12]	633 (11-25 y)	Wet or dry cough (96%), runny nose (83%), congestion (77%), postnasal drip (69%), sore throat (64%), watery eyes (59%), and headache (54%). Percent reporting: symptoms that required 4 of the 4 drug categories (57%), symptoms that required 3 of the 4 drug categories (29%). Percent reporting a symptom that required: an analgesic (88%), a decongestant (77%), an antihistamine (93%), an antitussive (83%).
Vicks Chemical Company 1978 [13]	322 (10 y or older)	45% experienced all 4 symptoms (nasal/head congestion, rhinorrhea, pain/fever/sore throat, and cough/phlegm) simultaneously on at least 1 day of their cold. 17% experienced all 4 symptoms simultaneously on 3 or more days of their cold. 56% experienced 3 of 4 symptoms on at least 1 day of their cold. Percent reporting: nasal/head congestion (85.1%), rhinorrhea (84.2%), pain/fever/sore throat (83.2%), cough/phlegm (64.3%).
Pagano 1983 [14]	1260 (0-17 y)	33% reported multiple symptoms of which 15% were cough/chest/nasal/throat, 15% were cough/chest/nasal, and 3% were cough/chest/sore throat.
2007 Ailment Diary 2008 [15]	671 (0-17 y)	Symptoms commonly reported: cough (76%), runny nose (63%), stuffy nose (37%). Most children reported 2 or more symptoms with 35% reporting 1 symptom only. Most frequently reported symptoms when: 1 symptom reported (coughing, 20%), 2 symptoms reported (coughing, 31%; runny nose, 24%; stuffy nose, 11%), 3 symptoms reported (coughing, 26%; runny nose, 26%; stuffy nose, 13%; chest congestion, 10%), 4 symptoms reported (coughing, 15%; runny nose, 16%; stuffy nose, 11%; sneezing, 11%), 5 or more symptoms reported (coughing, 12%; runny nose, 13%; stuffy nose, 11%; sneezing, 11%).
Gallup Survey 2008 [16]	759 (6 mo-11 y)	555 caregivers used OTC cough/cold medications for their children (70% multi-symptom). 391 caregivers used a multi-symptom cold medication to treat multiple symptoms at once for their child that contained a cough suppressant (72%), a decongestant (69%), a fever reducer/pain reliever (55%), an antihistamine (42%), and an expectorant (36%).

Abbreviations: mo = months, y = years

8.2.1.1 Summary of Cold Symptoms in Children From the Published Literature

A sore or scratchy throat is frequently reported as the most bothersome cold symptom on the first day of illness in children [1]. The sore throat resolves quickly and the second and third days yield nasal symptoms such as nasal obstruction, rhinorrhea, and sneezing [1]. Cough is associated with about 30% of colds and typically becomes the most bothersome symptom around the fourth or fifth day of illness [1]. The usual cold lasts about a week although 25% of colds in children last 2 weeks [1].

The incidence of colds due to rhinovirus during the first year of life has been reported as approximately 1.2 [2]. On average, preschool children have 5 to 7 colds per year; however, 10% to 15% of children have 12 or more colds per year [1]. The number of colds per year declines with increasing age, with an average of 2 to 3 colds per year in adulthood [1]. Young children in day care centers experience more colds than those in home care [1, 3]. Studies have also shown that children from birth to 12 years of age continue to experience cold symptoms 10 to 14 days after onset of a cold [3, 4, 11].

Pappas and colleagues evaluated symptom diaries kept for 81 healthy, school-age children (5 to 12 years old) for 10 days after onset of a cold [4]. Table 8-2 presents a summary of the cold symptoms experienced by these children. The 3 symptoms most frequently reported at onset, at their peak, and that persisted the longest were nasal congestion, runny nose, and cough. At their peak, nasal congestion, runny nose, and cough were reported by 88%, 72%, and 69% of children, respectively. Seventy-three percent of children remained symptomatic 10 days after onset of illness.

Table 8-2. Summary of Symptoms Experienced by Children Age 5-12 Years for 10 Days After Onset of a Cold – Pappas et al 2008 [4]

	Percent of Children Reporting		
Symptom[a]	Onset	Peak (Day)	Persisting Through (Day)
Nasal Congestion	59%	88% (Day 3)	≥75% (Day 7)
Runny Nose	~58%	72% (Day 3)	≥50% (Day 6)
Cough	46%	69% (Day 1)	≥50% (Day 8)
Sneezing	36%	55% (Day 1)	≥35% (Day 5)
Headache	15%	20% (Day 1)	15% (Day 4)
Feverishness	15%	15% (Day 1)	Declined over first 3 days

a: Sore throat and hoarseness were not evaluated.

Pappas and colleagues [4] compared the data for the subset of 37 children in their study with colds due to rhinovirus with data from a study by Gwaltney and colleagues of 137 rhinovirus colds in adults [5]. The progression of cold symptoms was comparable between adults and children, although minor differences were noted. Over 50% of children reported nasal congestion, runny nose, and cough during the first 5 days of illness, while the only symptom reported in over 50% of illnesses in adults was nasal discharge and that persisted only through Day 4. The duration of symptoms was longer in children than in adults; 73% of children were still reporting symptoms at Day 10 compared to 20% of adults. Cough in children peaked on Day 2 at over 70% and was reported in over 40% through Day 9,

compared to cough in adults, which peaked at about 40% on Days 3 through 5 and then dropped to about 10% by Day 10.

Hay and colleagues conducted a prospective cohort study of 13,617 preschool children living in southwest England [6]. Parents or guardians were sent questionnaires when the child was 6, 18, 30, 42, and 57 months old regarding the occurrence of 14 symptoms and consultation with a doctor for those symptoms. The 14 symptoms were of a general nature but did include cold and cough. The symptoms of cold and cough were the 2 most prevalent symptoms reported for children and for which a doctor was consulted. Table 8-3 presents a summary of the percentages of children by age that experienced a cold or cough and the percent of children for whom a doctor was consulted. In each age group, a larger percentage of children experienced the symptom compared to the percentage of children for whom a doctor was consulted concerning that symptom. This suggests that the majority of children reporting cold or cough symptoms are treated for these without the aid of a doctor. This study also demonstrated that the majority of children less than 5 years of age experience cold (88% to 96%) or cough (65% to 92%) symptoms.

Table 8-3. Percentage of Children Experiencing Cough or Cold and For Whom a Doctor Was Consulted, by Age – Hay et al 2005 [6]

Symptom	< 6 months	6 to 17 months	18 to 29 months	30 to 41 months	42 to 56 months
Percentage of Children Experiencing Symptom					
Cold	88%	95%	94%	94%	96%
Cough	65%	84%	86%	88%	92%
Percentage of Children Experiencing Symptom for Whom a Doctor was Consulted					
Cold	40%	42%	34%	27%	29%
Cough	34%	21%	14%	12%	9%

A prospective, randomized, double-blind, placebo-controlled study was performed by Kurugol and colleagues to evaluate the effect of zinc sulfate in children who developed 2 or more symptoms of the common cold [7]. The median duration of symptoms before admission was 25 hours and the mean age of the children was 5.2 years (range 1-10 years). Symptoms experienced upon entry by 120 children included nasal drainage (94.2%), cough (89.2%), sore throat (69.2%), nasal congestion (61.7%), scratchy throat (55.8%), fever (52.5%), sneezing (48.3%), hoarseness (39.2%), headache (19.2%), and muscle ache (18.3%). This demonstrates that children with the common cold experience multiple symptoms within the first 24 to 48 hours of the common cold.

Butler and colleagues performed a prospective, randomized study to evaluate the effect of 4% sodium cromoglycate spray and normal saline spray administered intranasally in 290 children between 1 and 12 years of age presenting to a family doctor with a suspected acute viral infection of the upper respiratory tract, beginning within the previous 7 days [8]. The mean duration of symptoms before admission was 3.5 days and 3.0 days in the sodium cromoglycate and saline groups, respectively. The mean age of the children was 5.3 years and 5.1 years in the sodium cromoglycate and saline groups, respectively. Symptoms experienced upon entry included coryza (80%), cough (79%), increased temperature (54%), pharyngitis (49%), enlarged lymph nodes (46%), and malaise (45%). This study demonstrates that children age 1 to 12 years with upper respiratory tract infections are also experiencing multiple symptoms around day 3.

Vernacchio et al reported on the uses of cough and cold medication by US children during the period 1999 to 2006, based on data from the Slone Survey, a national random-digit-dial telephone survey of medication use [9]. Data were reported for 4267 children less than 18 years of age. For children 13 years of age or younger, a parent or guardian was interviewed; 82.2% of interviews were completed by a parent or guardian for children 14 through 17 years of age. Subjects were asked to report all prescription and OTC medications, vitamins and minerals, and herbals/supplements taken during the preceding 7 days, gathering the relevant containers whenever possible. Cough and cold medicines included oral medicines that contained 1 or more antitussive, decongestant, expectorant, or first-generation antihistamine (e.g., chlorpheniramine and diphenhydramine).

Of 4267 children less than 18 years old, 10.1% had used a cough and cold medicine in the previous week. The 1-week prevalence of use was 4.1% for antitussives, 6.3% for decongestants, 1.5% for expectorants, and 6.3% for first-generation antihistamines. Of the 489 products used by the 439 subjects, 35.8% were single-ingredient products and 64.2% were multiple-ingredient products. The multiple-ingredient products most commonly used were combinations of a decongestant and a first-generation antihistamine (15.5%) and combinations of an antitussive, a decongestant and a first-generation antihistamine (10.4%). Of the cough and cold combination products used by the children, 16% contained ingredients in 3 of the following 4 categories: antitussive, antihistamine, decongestant, analgesic. The reason given for use of the 489 products was cough (23.7%), cold (21.7%), allergy (19.6%), and not related to cough, cold, or allergy or unclear (35.0%).

Figure 8-1 summarizes the 1-week prevalence of use of antitussive, decongestant, expectorant, and first-generation antihistamine by age group. Use of antitussives, decongestants, and first-generation antihistamines was highest among children 2 to 5 years of age followed by children less than 2 years.

The data from this survey reinforce that children less than 18 years of age use multiple-ingredient products frequently, with almost half of the respondents reporting use for cough and cold.

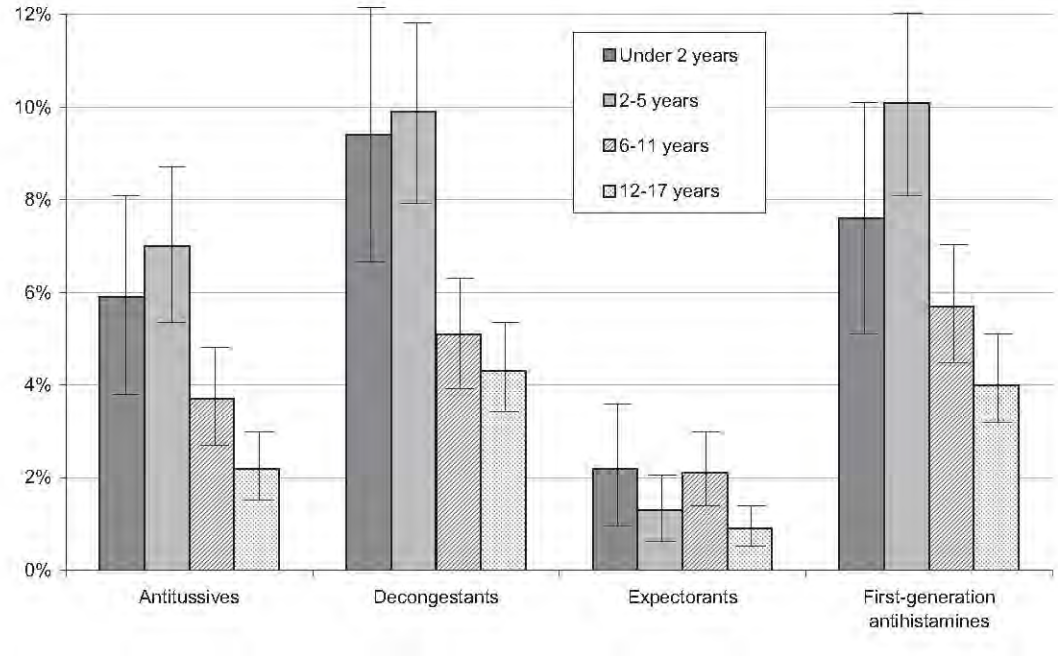

Figure 8-1. Prevalence of Exposure to Antitussive, Decongestant, Expectorant, and First-Generation Antihistamine Active Ingredients According to Age Group. Bars Represent 95% CIs [reprinted from Vernacchio et al 2008 [9]].

8.2.1.2 Summary of Cold Symptoms in Children From Unpublished Reports

An unpublished report on the use of cough and cold medication based on Slone Survey data obtained from subjects interviewed between February 1998 and April 2007 included data for 2857 children ages 0 to 11 years [10]. During this period, it was reported that in a given week 12.0% of children less than 2 years of age, 12.0% of children 2 to 5 years of age, and 8.5% of children ages 6 through 11 years used a cough and cold medication. Antihistamines and antitussives were most frequently used by children aged 2 to 5 years (8.3% and 6.5%, respectively), whereas decongestant use was most common in children less than 2 years of age (7.8%). Expectorant use was relatively uncommon in all age groups, with a range of 1% to 2%. Overall, it was reported that 1 cough and cold medication was used by 93.7% of children, of which 64.1% was a multiple-ingredient product. When children less than 2 years of age were further classified into 3 age groups (<6 month, 6 to 11 months, and 12 to 23 months), antihistamine, antitussive, and expectorant use was most common in those age 12 to 23 months, while the highest prevalence of decongestant use was in children 6 to 11 months. Use of any cough and

cold medication was reported for 6.2% of infants <6 months old, 16% of those 6 to 11 months, and 12% of those 12 to 23 months old. The data from this survey indicate that multiple-ingredient cough and cold medicines are frequently used in children from birth to age 11 years.

A survey by Vicks Research Center cited in the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Products (CCABADP) final monograph evaluated children who went to a pediatrician and were diagnosed with upper respiratory tract infections. Overall, 3166 children age 2 to 12 years in 14 cities across the United States from December 1981 to April 1982 were included [11]. The mother of the child described the type and duration of each symptom and the remedies currently being used when the pediatrician was contacted. The pediatrician also documented all physical findings pertinent to upper respiratory infection upon evaluation. Of the 3166 children, 65.2% were between 2 and 5 years of age and 34.8% were between 6 and 12 years of age. Approximately 3% of the 3166 children had symptoms, especially cough, lasting longer than 2 weeks. This study was concerned with acute upper respiratory infections, which were defined as those infections with symptoms that were present for fewer than 14 days. For this reason, the analyses of duration of each symptom were limited to the population of children with symptoms present for fewer than 14 days. In this subgroup, the median duration of each symptom was 2 or 3 days (except for earache, which was 1 day). Table 8-4 summarizes the symptoms reported by mothers and the clinical findings noted by the pediatricians. The most frequent symptoms reported by mothers were any cough (60.2%), fever (56.4%), runny nose (42.2%), sore throat (34.4%), and earache (32.8%). The most frequent clinical findings by physicians were any cough (48.5%), nasal congestion (47.7%), pharyngitis (46.7%), fever (44.2%), and rhinorrhea (43.3%). Physicians found that children age 2 to 5 years more frequently experienced rhinorrhea (49.6% compared to 31.5% in older children) and otitis media (40.8% compared to 24.7% in older children) while children age 6 to 12 years more frequently experienced pharyngitis (58.4% compared to 40.5% in younger children). These findings were similar to those symptoms reported by mothers. Physicians found cough with nasal congestion and cough with rhinorrhea accounted for the most frequent combinations of clinical findings (28.9% and 27.3%, respectively). Mothers found cough with fever and cough with runny nose accounted for the most frequent combinations of symptoms (occurring in 33.6% and 30.5% of all children, respectively).

Table 8-4. Percent of Children with URI Symptoms Reported by Mothers and Percent of Children with URI Clinical Findings by Physicians – Vicks Research Center 1983 [11]

Symptom	% Children Age 2-5 y Reported by Mothers/Physicians (N=2064/1889)	% Children Age 6-12 y Reported by Mothers/Physicians (N=1102/1005)	% All Children Reported by Mothers/Physicians (N=3166/2894)
Any cough (wet or dry)	64.5/51.8	52.3/42.3	60.2/48.5
Nasal congestion	--/50.5	--/42.5	--/47.7
Fever	55.1/45.4	58.3/42.0	56.4/44.2
Runny nose/ rhinorrhea	48.3/49.6	30.7/31.5	42.2/43.3
Dry Cough	34.6/23.5	35.4/26.4	34.9/24.5
Sore Throat/ Pharyngitis	23.8/40.5	54.2/58.4	34.4/46.7
Earache/ Otitis media	34.9/40.8	28.9/24.7	32.8/35.2
Wet cough	34.1/32.1	20.2/19.6	29.3/27.7
Headache	10.1/--	22.8/--	14.5/--
Bronchitis	--/7.7	--/6.3	--/7.2
Hoarseness/ Laryngitis	11.0/6.1	7.3/7.0	9.7/6.4
Swollen glands/ lymphadenopathy	7.7/22.6	9.5/28.7	8.3/24.7
Prolonged Expirations	--/5.1	--/5.0	--/5.1
Wheezing	--/4.1	--/4.0	--/4.0
Tracheitis	--/4.1	--/3.5	--/3.9
Pneumonia	--/3.6	--/3.0	--/3.4
Other	19.7/--	20.1/--	19.8/--

Abbreviations: URI = upper respiratory infection, -- = not recorded by mother or physician, y = years.

A survey by Bristol Myers Products cited in the CCABADP final monograph reviewed the records of 1000 patients with common cold, who had been accepted for pharmacological assay studies during the months of December, January, and February in 1976 through 1979 [12]. At their time of entry into the assay studies, patients were asked to complete a questionnaire that described their current cold using a checklist of symptoms. Of the 1000 patients ages 11 years and older, 57% had 4 or more symptoms treatable with medicines containing ingredients in each of the 4 drug treatment categories (decongestant, analgesic, antihistamine, antitussive). Another 30% would have required drugs from 3 of the 4 drug treatment categories. Symptoms reported by patients were evaluated overall and by age, duration of the cold, sex, and allergic history. The most frequently reported symptoms for

the 633 patients age 11 to 25 years were wet or dry cough (96%), runny nose (83%), congestion (77%), postnasal drip (69%), sore throat (64%), watery eyes (59%), and headache (54%). Of the 633 patients age 11 to 25 years, 57% had 4 or more symptoms treatable with medicines containing ingredients in each of the 4 drug treatment categories and 29% had symptoms that required 3 of the 4 drug treatment categories. For patients age 11 to 25 years, 88% reported a symptom that required an analgesic, 77% reported a symptom that required a decongestant, 93% reported a symptom that required an antihistamine, and 83% reported a symptom that required an antitussive.

A total of 322 people, 10 years or older, suffering from colds were contacted by telephone using a random-digit dial technique in a consumer survey by Vicks Chemical Company cited in the CCABADP final monograph [13]. Interviews were conducted during the cold seasons between mid-September 1976 through mid-April 1977 and mid-September 1977 through mid-November 1977. Cold sufferers were asked to identify symptoms they had experienced from a list of symptoms and then respond to a question for each symptom as to whether it was bothersome enough for them to want relief. Overall, 45% of all cold sufferers experienced all 4 symptoms (nasal/head congestion, rhinorrhea, cough/phlegm, and pain/fever/sore throat) simultaneously on at least 1 day of their cold. All 4 symptoms were experienced simultaneously on 3 or more days of their cold by 17% of cold sufferers. Three of the 4 symptoms were experienced by 56.1% of cold sufferers. Thirty percent of cold sufferers reported their colds were severe enough that they needed relief from all 4 symptoms simultaneously on at least 1 day, while 10% of cold sufferers needed relief from all 4 symptoms during 3 or more days. Overall, 85.1% of sufferers reported nasal/head congestion, 84.2% reported rhinorrhea, 83.2% reported pain/fever/sore throat, and 64.3% reported cough/phlegm. Over the course of 7 days, nasal/head congestion decreased from 79.2% to 19.9%, rhinorrhea decreased from 79.5% to 15.5%, pain/fever/sore throat decreased from 77.0% to 10.9%, and cough/phlegm decreased from 52.2% to 20.2%. On day 7, 12.5% of cold sufferers were still experiencing all 4 symptoms.

Pagano conducted a consumer survey cited in the CCABADP final monograph of 2297 adults and 1423 children birth to 17 years of age suffering from cold or flu in 1982 and 1983 [14]. This National Colds/Flu Incidence Survey was a telephone survey that used a random-digit dial technique. The survey gathered information weekly each year between mid-September and mid-April. Cold sufferers included 1942 adults and 1260 children (newborns to 17 years of age). Of the 1260 children, 33% reported multiple symptoms of which 15% were coughing/chest congestion/nasal congestion/sore throat, 15% were coughing/chest congestion/nasal congestion, and 3% were coughing/chest congestion/sore throat.

The 2007 Ailment Diary used online methodology via the TNS NFO MySurvey Community to survey nationally representative households [15]. A daily diary was filled out for

individuals within an entire household for a 4-week period. Information was collected for up to 10 members in each household. Each week, respondents reported all symptoms experienced by any household member for 7 days and any treatment (medical, alternative, or nonmedical) used. Additionally, any OTC or prescription medication taken for preventive purposes was reported. Occasion-level data were obtained from the 2007 Ailment Diary database for household members less than 18 years of age for whom an OTC children's medication was taken to treat upper respiratory symptoms due to a cold. The sample consisted of 671 children from birth to 17 years of age. Of the 671 children, 87 were less than 1 year old, 161 were age 2 to 3 years, 208 were 4 to 6 years, 121 were 7 to 9 years, 74 were 10 to 12 years, and 20 were 13 to 17 years. The 3 most frequently reported symptoms in children suffering from a cold were cough (76%), runny nose (63%), and stuffy nose (37%). Table 8-5 presents the number of upper respiratory symptoms experienced in combination by children with a cold. Most children reported 2 or more symptoms when they had a cold, with 35% reporting 1 symptom only.

Table 8-5. Percentage of Children Ages 0 to 17 Years With a Cold by Number of Upper Respiratory Symptoms Experienced – 2007 Ailment Diary [15]

Number of Upper Respiratory Symptoms Experienced	Percent of Children[a] (N=671)
1	35
2	42
3	33
4	18
5+	14

a: Percentages add to more than 100% as an individual may have 1 symptom on 1 occasion and 2 or 3 symptoms on another occasion.

Table 8-6 presents the single and multiple upper respiratory symptoms experienced by children from newborn to age 17 years with a cold by number of symptoms experienced. Coughing was the most frequently reported symptom (20%) when only 1 symptom was reported. Coughing (31%), runny nose (24%), and stuffy nose (11%) were the most commonly reported symptoms when 2 symptoms were reported. Coughing (26%), runny nose (26%), stuffy nose (13%), and chest congestion (10%) were the most commonly reported symptoms when 3 symptoms were reported. Coughing (15%), runny nose (16%), stuffy nose (11%), and sneezing (11%) were the most commonly reported symptoms when 4 symptoms were reported. Coughing (12%), runny nose (13%), stuffy nose (11%), and sneezing (11%) were the most commonly reported symptoms when 5 or more symptoms were reported.

Table 8-6. Percent of Children Ages 0 to 17 Years With a Cold by Upper Respiratory Symptom and Number of Symptoms Experienced – 2007 Ailment Diary [15]

UR Symptoms	Total (N=732) %	Only One UR Symptom %	Two UR Symptoms %	Three UR Symptoms %	Four UR Symptoms %	Five or More UR Symptoms %
Total		35	42	33	18	14
Coughing	76	20	31	26	15	12
Runny nose	63	8	24	26	16	13
Stuffy nose	37	5	11	13	11	11
Chest congestion	28	1	9	10	6	8
Sneezing	26	0	4	9	11	11
Sore throat	20	1	5	7	4	6
Sinus/head congestion	16	1	4	5	4	6
Itchy/watery eyes	15	0	2	4	5	7
Post nasal drip	10	0	1	3	2	5
Sinus pressure/pain	8	0	1	2	1	5
Irritated/dry throat	4	0	0	1	1	2
Tight chest/wheezing	3	0	0	1	1	1
Other nose/throat/ chest/eyes/ears	2	0	0	0	0	1

Abbreviations: UR = Upper respiratory

The 2008 Gallup Survey was conducted online in a national sample of 759 primary caregivers of children 6 months to 11 years [16]. Overall, there were 99 children age 6 to 23 months, 279 children 2 to 5 years, and 381 children 6 to 11 years. The majority (82%) of the children had 1 to 4 colds within the past 12 months. Overall, 72% of caregivers gave their child an OTC cough/cold medication. Use of OTC cough and cold medications became more prevalent in older children, with cough and cold medications used in 79% of children 6 to 11 years and 73% of children 2 to 5 years compared to 47% of children 6 to 23 months. As shown in Table 8-7, of 555 caregivers who used OTC cough and cold medications for their children, 70% used a multi-symptom cold medication to treat multiple symptoms at once for their most recent cold. A smaller percentage of caregivers (55%) gave their 6- to 23-month-old children a multi-symptom cold medication to treat multiple symptoms compared to caregivers of children 2 to 5 years old (73%) and children 6 to 11 years old (70%). These findings support the CHPA Pediatric Task Force position that the availability of both single- and combination-ingredient products provides the benefit of targeting the specific symptoms of a child's cold and that children commonly develop colds with 1 or more symptoms including nasal congestion, cough, runny nose and either pain or fever.

Table 8-7. Percent of Children Using Various Types of OTC Cough and Cold Medication During the Most Recent Cold – 2008 Gallup Survey [16]

Type of Cough/Cold Medication	Total Primary Caregivers (N=555) %	Child's Age		
		6-23 months (N=44[a]) %	2-5 y (N=204) %	6-11 y (N=307) %
A multi-symptom cold medication to treat multiple symptoms at once	70	55	73	70
A single-symptom cough suppressant to quiet or reduce cough	19	23	19	19
A single-symptom decongestant to relieve stuffy nose	15	23	15	14
A single-symptom expectorant to loosen phlegm/clear chest congestion	8	21	5	8
A single-symptom antihistamine to dry up a runny nose	6	4	9	5
Not sure	4	10	2	4

a: Sample size (n=44) too small for statistical reliability.

Furthermore, for the 391 caregivers who used a multi-symptom cold medication to treat multiple symptoms at once for their child, the cold medication contained a cough suppressant (72%), a decongestant (69%), a fever reducer/pain reliever (55%), an antihistamine (42%), and an expectorant (36%). This also supports that children with colds experience multiple symptoms.

8.2.1.3 Summary

In summary, children frequently develop colds with one or more symptoms including nasal congestion, cough, runny nose (rhinorrhea), pain, and fever. The majority of children experience multiple symptoms concurrently. Use of multiple-ingredient medicines to treat these symptoms in children has been reported to range from 64% to 70% [9,10,16]. The percentage of older children (10 years and older) with four or more symptoms treatable with medicines containing ingredients in each of the four categories (antitussive, antihistamine, decongestant, analgesic) has been reported to range from 45% to 57% [12,13]. In addition, the percentage of children (all ages) with symptoms treatable with medicines containing ingredients in three of the four categories has been reported to range from 16% to 56% [9,12,13]. Cough was the most frequently reported symptom in children regardless of whether it was reported alone or in combination with other symptoms [15].

8.2.2 Treating Symptom Complexes

Having both single- and combination-ingredient products available is beneficial to caregivers, because they can treat the specific symptoms of a child's cold. As summarized in Section 8.2.1, cold symptoms in children vary in number and type, and in which symptoms occur in combination. The availability of product choices with various combinations of cough and cold ingredients allows parents and caregivers to tailor treatment to their child's specific cold symptoms. In addition, combination products make it easier to administer treatments to children; parents and caregivers can use 1 product to treat multiple symptoms instead of using multiple products to treat multiple symptoms. Children are more likely to be compliant with taking 1 combination product than with taking multiple single-ingredient products, which likely translates into better relief of the cold symptom complex.

8.2.3 Simplified Medication Administration

The use of combination products reduces the likelihood of dosing errors since parents administer 1 product, instead of several products, to their child for relief of all of their symptoms. The use of combination products eliminates the need for parents to review and understand the dosing and Drug Facts on multiple products, some of which may have different dosing intervals. This simplifies medication administration, thus reducing the opportunity for dosing errors.

8.2.4 Similar Safety Profile for Single-Ingredient and Combination Products

Single-ingredient and combination-ingredient pediatric cough and cold products have similar safety profiles, with a very rare occurrence of serious adverse events. Section 8.2.4.1 provides a summary of reporting rates for serious nonfatal adverse events from the McNeil post-marketing adverse event data for cough and cold ingredients combined for a 6.5-year period from January 2000 through June 2007.

8.2.4.1 McNeil Post-Marketing Data for Cough-Cold Ingredients Combined – Nonfatal Serious Adverse Events

Data concerning combined pediatric cough and cold serious nonfatal adverse events were summarized in the CHPA presentation at the October 2, 2008 Part 15 Hearing. As shown in Table 8-8, these data indicate that serious nonfatal adverse event reporting rates are very low and similar for single-ingredient and combination products. Reports of serious nonfatal adverse events were obtained from the McNeil post-marketing adverse event databases for the period from January 2000 through June 2007. Exposure was based on sales of McNeil Consumer Healthcare medicines for the same period as available through IMS Health NSP data. The age distribution was estimated based on use of OTC medicines

for cough/cold by children in the United States from the Slone Epidemiology Center and United States census data from 2000 [17,18].

Table 8-8. Reporting Rates for Cases Coded as Serious and Nonfatal (Excluding Accidental Ingestion) per Million Doses Distributed, McNeil Consumer Healthcare Post-marketing Database, January 2000 – June 2007

	Pediatric Age Group	
	2 to < 6 years	6 to <12 years
All pediatric OTC cough and cold medicines	0.05	0.03
Single ingredient	0.05	0.04
Combination ingredient	0.04	0.03

8.3 Providers Treat Colds with Both Single and Combination Products

Caregivers and healthcare providers currently use both single-ingredient and combination-ingredient cough and cold products when treating children with colds when 1 or more symptoms are present.

8.3.1 Pediatrician Recommendations for Children Less Than 12 Years of Age

Pediatricians recommend both single-ingredient and combination-ingredient cough and cold medicines for children less than 12 years of age. Figure 8-2 provides average numbers of weekly recommendations by pediatricians for the 12-month period ending July 31, 2008, based on IMS NDTI data. These data are presented for single-ingredient and combination cough and cold products for ages 2 to <6 years and 6 to <12 years. These data show that pediatricians working in outpatient and ambulatory care settings continue to recommend cough and cold medicines for children less than 12 years of age. These data also show that pediatricians recommend combination products more commonly than single-ingredient products.

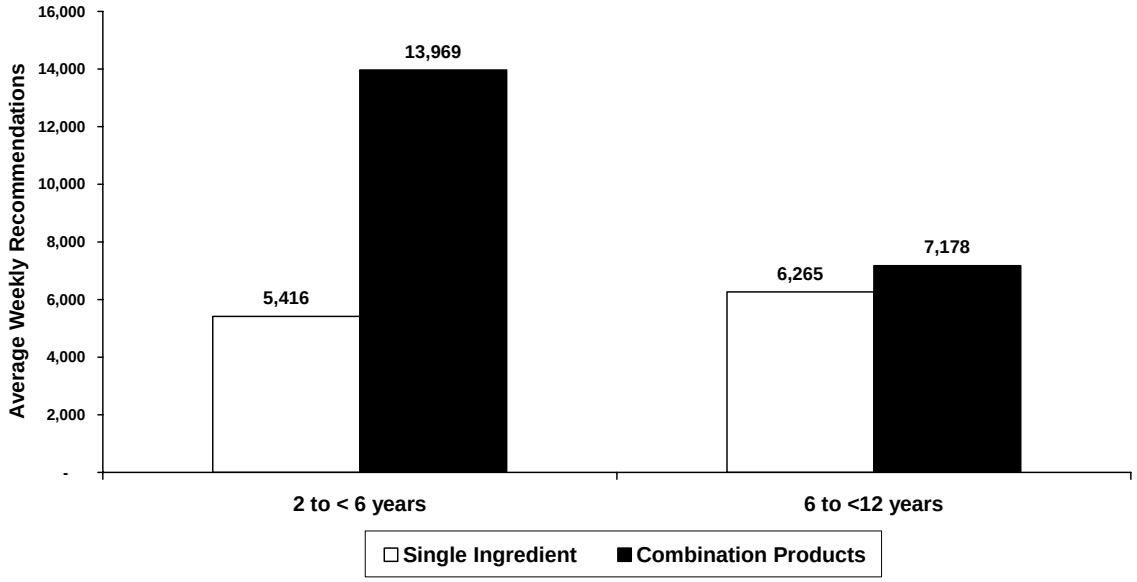

Figure 8-2. Average Weekly Pediatrician Recommendations for the 12-month Period Ending July 31, 2009, IMS NDTI Data

8.3.2 Caregivers Report Appropriate Use of Products

Parents appropriately use both single- and combination-ingredient OTC cough and cold medicines. An unpublished report on the use of cough and cold medication based on data from the Slone Survey, a national random-digit-dial telephone survey of medication use, obtained information from subjects interviewed between February 1998 and April 2007 and included data for 2857 children ages 0 to 11 years [10]. Parents were asked to report all prescription and OTC medications, vitamins and minerals, and herbals/supplements taken by their children during the preceding 7 days, gathering the relevant containers whenever possible. Cough and cold medications included oral medications that contained 1 or more antitussive, decongestant, expectorant, or first-generation antihistamine (e.g., chlorpheniramine and diphenhydramine). During this period, it was reported that in a given week 12.0% of children less than 2 years of age, 12.0% of children 2 to 5 years of age, and 8.5% of children ages 6 through 11 years used a cough and cold medication. Overall, it was reported that 1 cough and cold medication was used by 93.7% of children, of which 64.1% was a multiple-ingredient product. Two to 3 days of use of cough and cold medication per week was the most frequent category of duration of use reported, with percentages of children in this category ranging from 47.1% to 60.0% for various categories of cough and cold medications (antihistamine, decongestant, antitussive, and expectorant). Use for 7 days per week was relatively infrequent, and ranged from 4.5% to 10.2%.

8.4 Efficacy and Safety of Combination Cough and Cold Products

It is unnecessary to confirm efficacy and safety of every combination cough and cold product when scientific data are available for the individual cough and cold ingredients consistent with FDA's OTC combination drug policy.

8.4.1 Summary and Impact of OTC Combination Policy

As a general principle of FDA's OTC drug combination policy, when effectiveness and safety data are available for individual ingredients, additional study of the combination of ingredients is not needed to confirm efficacy and safety. The OTC drug combination policy, at 21 CFR 330.10 (a) (4) (iv), states the following:

> *"An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population."*

The 1976 Advisory Review Panel on OTC CCABADP applied the OTC Drug Combination Policy when it considered the place of combination products in the marketplace during its deliberations to establish the CCABADP monograph. The panel limited each Category I[1] combination to one active ingredient from any one pharmacologic group, to reduce the likelihood of a competitive or potentiating effect between agents [41 FR 38322]. The Panel also limited combinations to three pharmacologic groups, as it was unable to identify a target population that could benefit from a combination product containing four or more pharmacologic groups [41 FR 38323]. The Panel indicated that the combination products should clearly indicate in their labeling that they are to be used only when multiple symptoms are present concurrently [41 FR 38322].

On November 21, 1978 [Docket 78D-0322], FDA announced the availability of a "General Guideline for OTC Drug Combination Products," which included conditions pertaining to combinations of Category I active ingredients from the same and different therapeutic categories, as long as the combination met all of the requirements of the OTC Drug Review Regulation [21 CFR 330.10 (a) (4) (iv)]. The guideline also included conditions for

[1] Category I represents conditions that will be included in the monograph

combinations of Category I active ingredients from the same therapeutic category with the same or different mechanisms of action.

During the rulemaking process to finalize the Combination Drug Products segment of the CCABADP monograph, one comment reviewed in the 1988 Tentative Final Monograph (TFM) stated that cough-cold products contain “active chemicals” (both “therapeutic ingredients and cosmetic chemicals such as flavors and dyes”) and argued that the safety of combination cough-cold products depends not only on the safety of individual ingredients for individual symptoms, but also on the safety of the ingredients taken together, and challenged that the Advisory Review Panel’s endorsement of combination products did not meet “normal FDA standards” [53 FR 30533]. The agency disagreed with this comment, and stated that the panel’s review of combination products followed FDA standards at 21 CFR 330.10 (a) (4) (iv), described above. The agency referred to a recommendation by the Advisory Review Panel that only active and inactive ingredients essential to a product should be included in marketed products. The agency further stated that the panel considered medical rationale and drug interactions when making its recommendations for combination products. The agency concluded that the panel’s recommendation and the agency’s “General Guideline for OTC Drug Combination Products” adequately addressed the comment’s concern as to the continued marketing of products containing several “active chemicals” and the safety of these ingredients when taken together in a combination drug product.

In the 1988 TFM, the agency commented that combinations of cough-cold ingredients specified in the TFM provide a convenient and rational approach for relief of concurrent symptoms which so frequently accompany the common cold, and that combination products formulated in accordance with the TFM would be safe and effective in a large percentage of the general population [53 FR 30534]. Additionally, the agency placed no fixed limit upon the number of active ingredients in a combination product if it could be shown to be a rational, safe and effective combination with a suitable target population.

When the CCABADP monograph was finalized in December 2002, the agency included numerous combinations as GRASE [67 FR 78165]. All of the OTC pediatric combination cough-cold medicines currently marketed by CHPA member companies for the treatment of children 4 years of age and older are included in the CCABADP monograph.

8.4.2 History of Safe Use of OTC Monograph Combination Products

OTC monograph combination medicines have a long history of safe use at therapeutic doses. Thus, unless there is a specific scientific concern for a given combination, additional safety studies are not needed. As summarized in Section 8.2.4, single-ingredient and combination-ingredient pediatric cough and cold products have similar safety profiles with a very rare occurrence of serious adverse events.

8.4.3 Pediatric Research to Answer New and Relevant Scientific Questions

Research in children should be performed only when necessary to answer new and relevant scientific questions. It is important to be sure that a study is required and appropriate for children before it is conducted in this vulnerable population.

Increased knowledge and awareness of differences in physiology of children combined with off-label use of drugs in children have led to legislation and regulation that support and encourage pediatric research as part of the general drug development process. These include the 1994 Pediatric Final Rule, the provision for pediatric exclusivity as part of the 1997 FDA Modernization Act (FDAMA), the 2002 Best Pharmaceuticals for Children Act (BPCA), the 2003 Pediatric Research Equity Act (PREA), and the 2007 renewal of BPCA and PREA in the United States. This legislation has contributed to increases in pediatric clinical research conducted by the pharmaceutical industry.

The objectives of our pediatric research program are to confirm or refine pediatric doses, reaffirm pediatric effectiveness in treating symptoms, and to further support pediatric safety. These objectives will be accomplished by integrating existing or historical data with new pediatric pharmacokinetic and effectiveness data, and by bridging historical effectiveness data with new pharmacokinetic and/or pharmacodynamic data.

Consistent with FDA's OTC combination policy summarized in Section 8.4.1, if new effectiveness data are generated for single ingredients in children, pediatric efficacy studies for combination products comprised of these ingredients would not be necessary. Alternatively, if single ingredients have been shown to be effective in adults, it may be reasonable to confirm the effectiveness in children of individual ingredients as part of a combination, especially when the cold symptoms commonly occur concurrently and each ingredient relieves different symptoms. This can be accomplished with composite- and single-symptom scores as endpoints.

8.5 Summary

Children commonly develop acute respiratory tract infections (colds) with one or more symptoms including nasal congestion, cough, runny nose, pain, and fever. Caregivers and healthcare providers currently use both single ingredient and combination ingredient products when treating children with colds when one or more symptoms are present. Combinations of pediatric cough and cold ingredients should remain available for children ages 4 years and older because they address the need for treatment of simultaneous cold symptoms and have the potential to reduce the number of dosing errors. In the course of the pediatric research program, it is unnecessary to confirm safety and efficacy of every combination product when scientific data are available for the individual ingredients in children or adults consistent with FDA's OTC combination drug policy.

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Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to Question 9

FDA Question:

"Can measurement errors in dosing be reduced using more standardized measuring devices or alternative dosage forms, and if so, what is the best way to effect this change?"

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

RESPONSE TO FDA QUESTION 9

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9 FDA QUSETION 9

"Can measurement errors in dosing be reduced using more standardized measuring devices or alternative dosage forms, and if so, what is the best way to effect this change?"

9.1 Position of the CHPA Pediatric Task Force

The leading makers of children's over-the-counter (OTC) cough and cold medicines are committed to working with FDA, CDC, and other experts in the field to ensure that parents and caregivers have appropriate treatment choices for their children, accurate tools with which to administer medications while limiting dosing errors, and child-resistant packaging to prevent accidental ingestions.

- To be accurate, measuring devices and alternative dosage forms must be tailored to the physico-chemical characteristics and dosing recommendations of a specific product. There is not one solution for all products, and one standard measuring device would not necessarily reduce measurement errors. Approaches to harmonize specific elements of measuring devices must be evaluated for their effectiveness before their introduction with products in the marketplace.
- Manufacturers of oral OTC pediatric cough and cold medicines are continually improving both the design and implementation of packaging to further increase accurate dosing by caregivers and parents, including providing product-specific devices that are easier to read and use where the units are consistent with the labeled dosing instructions.
- Consumer education on the appropriate use of dosing devices and administration may help decrease medication errors, and some of these elements are incorporated in the current multiyear pediatric education program.
- No data are available that demonstrate the effects of alternate dosage forms on measurement errors with pediatric cough and cold medicines.

9.2 Medication Dosing Errors

9.2.1 Results from the National Poison Data System Regarding Measurement Errors

Measurement errors with pediatric cough and cold medicines have been reported. Results from the most recent report of the American Association of Poison Control Centers,[1]

[1] The American Association of Poison Control Center (AAPCC) maintains the National Poison Data Base (NPDS), which is the only comprehensive poisoning surveillance database in the United States

Bronstein et al.[1] showed that 60.6% of unintentional exposures occurred in children younger than 6 years and included errors such as “inadvertently took/given medication twice, took incorrect dose, confused units of measure, dispensing cup error.” In 2006, cough/cold products (5.7%) were among the top categories for reported pediatric (5 years or younger) exposures based on the total number of reported exposures in children.

9.2.2 Results from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project Regarding Measurement Errors

Schaefer et al. [2] reported data for 2 years (collected from January 1, 2004, through December 31, 2005) from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES) project, a nationally stratified sample of 63 hospitals in the United States and its territories with a minimum of 6 beds and a 24-hour emergency room (ER). An estimated 7,091 patients under 12 years old were treated in ERs for adverse drug effects from cough and cold medications, accounting for 5.7% of ER visits for all medications in this age group. Most ER visits (64%) were attributed to cough and cold medications in children aged 2 to 5 years.

- Unsupervised ingestions of cough and cold medications were responsible for two-thirds (66%) of the ER visits, substantially higher than for other medications.
- Twenty-six percent of ER visits were due to supervised administrations without documented medication errors.
- Eight percent of ER cases were due to supervised administrations with documented medication errors.

Most errors occurred in children under 2 years followed by children to 2 to 5 years of age. The predominat type of medication error in children under 2 years, for whom labels do not specify doses, was the administration of excess doses. In children 2 to 5 years of age, confusion about units of measure was the main reason for errors.

9.2.3 Other Available Data on Sources of Measurement Errors

Many OTC medicines, particularly those products marketed for use in children, are available as liquid formulations that require measurement for dosing. The available data

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with annual reports available from 1983. The information included in its annual reports reflects the information submitted by the regional poison control centers into the NPDS. As of the most recent report from 2006, 60 of the nation's 61 US poison centers upload case data automatically. Most upload every 1-60 minutes (median 11 minutes) to NPDS creating a real-time national exposure database and surveillance system [1] . These data are used to identify hazards early, focus prevention education, guide clinical research, direct training, and detect chemical and bioterrorism incidents. AAPCC data have prompted product reformulations, repackaging, recalls, and bans; are used to support regulatory actions; and contribute to post-marketing surveillance on newly released drugs and products.

demonstrate that measurement errors occur through the use of measurement devices not supplied with the product or because of confusion associated with dosing devices.

9.2.3.1 Available Data on the Use of non-Product Specific Measurement Devices as a Source of Medication Errors

Dosing of liquid medicines requires the use of a measuring device. Devices used for measurement of liquid medicines include household spoons, oral syringes, oral droppers, medicine cups, and cylindrical spoons. These devices may or may not be calibrated in a manner suitable for pediatric cough and cold medicines.

Studies have found that many caregivers of pediatric patients use nonstandardized dosing devices [3,4,5,6,7,8], which can contribute to medication errors. Several studies have attributed inappropriate dosing of a medicine to children to use of the household teaspoon as a measuring device [5,6,8,9].

An evaluation of liquid-dosing devices available in participants' homes (the household teaspoon, medicine cup, cylindrical spoon, oral dosing syringe, oral dropper, measuring spoon, and baby dispenser) found that the household teaspoon was the device most frequently used (73%) for measuring liquid medicines [4]. The most frequent error (70%) occurred when the participants mistakenly measured 1 teaspoon instead of 1 tablespoon. Accuracy of dosing and knowledge regarding weight-based dosing was significantly correlated with the participant's education level, similar to what was found in other studies [3,10].

9.2.3.2 Authoratative Bodies Do No Support the Use of Teaspoons as Dosing Devices

In 1975 the American Academy of Pediatrics (AAP) issued a statement addressing inaccuracies in administering liquid medications and advising on the use of appropriate liquid administration devices [11]. The United States Pharmacopeia (USP) standard <1221> for teaspoons cautions that household spoons are not accurate measuring devices and that the actual volume contained and delivered from a spoon depends on the physico-chemical nature of the product, including viscosity and surface tension [12]. A dosing device specifically calibrated for the product and provided with it is recommended for accurate dosing.

9.2.3.3 Available Data on Medication Errors with the Use of Dosing Cups as Measurement Devices

Dispensing cups are provided with many OTC medicines. However, studies have shown that consumers may have difficulty using these devices appropriately. In some cases,

consumers inappropriately assume that one dose is a full dispensing cup or that a full dispensing cup is the unit of measure [13,14]. Other sources of error associated with the use of dispensing cups include confusion between “teaspoon” and “tablespoon” and use of the dispensing cup intended for one product with another product [4,13,15].

9.3 Product and Education Changes by Manufacturers

Although most OTC pediatric products are provided with product-specific dosing devices, manufacturers have committed to moving forward to ensure that all pediatric liquid cough and cold products will have product-specific dosing devices. This effort will help to decrease the use of nonstandard or non-product-specific dosing devices. Manufacturers of oral OTC pediatric cough and cold medicines are continually improving both the design and implementation of packaging to further increase accurate dosing by caregivers and parents, including providing product-specific devices that are easier to read and use where the units are consistent with the labeled dosing instructions.

Results from several other studies emphasize the benefit of improved caregiver education on the accuracy of dosing medication to children [9,13,16,17]. Several studies have demonstrated that factors independent of the device itself may also have an impact on appropriate use of a liquid medication device. It has been shown that individuals who receive education on how to use oral administration devices are more likely to accurately measure liquid medications [8, 10]. Gribetz and Cronley [16] observed that that many individuals inappropriately used the administration device intended for a product of one concentration for the measurement of a product with a different concentration. A recent study reported that plain language and use of a pictogram resulted in less liquid medicine dosing errors by caregivers and parents of young children (30 days to 8 years of age) [18]. There were fewer errors in dosing accuracy compared to the number of errors by those who received standard counseling for daily doses (5.4% vs 47.8%), and improvements were observed in knowledge of appropriate medicine preparation and dosing frequency [18].

While efforts are underway to determine the root causes of measurement errors and volumetric variabilities, CHPA has incorporated messages into its multiyear education campaign for safe use of pediatric medications, including the recommendation to use the measuring device that comes with a product.

9.4 Coordinated Efforts to Prevent Unsupervised Ingestions and Unintentional Overdoses in Children

OTC drug manufacturers are not alone in the efforts to prevent unsupervised ingestions by children. On November 13-14, 2008, CDC hosted a stakeholder meeting [19] focused on prevention strategies against unintentional overdoses and unsupervised ingestions, two types of exposure associated with adverse events with OTC children’s medicines. These

adverse events were identified in the NEISS-CADES database (see Section 9.2.2). There are more reports of unsupervised ingestions than of medication errors as reasons for ER visits. Attendees from federal agencies, academia, industry, poison control centers, and professional organizations identified the following focus areas for further exploration:

- Understand the root-cause leading to the specific circumstances under which children ingest either liquid or solid medicines outside of their parent's and other caregiver's supervision or under which caregivers give children incorrect doses.
- Identify ways to decrease the variability of volumetric measurements to help parents and other caregivers understand recommended doses and successfully administer medicines to their children.
- Develop packaging innovations designed to limit access to multiple doses and therefore reduce the potential for harm in overdose and unsupervised ingestion situations.
- Develop a few key messages for dissemination by all stakeholders through public health education efforts to address unsupervised ingestions and medication errors.

CHPA and its member companies are committed to these focus areas and will work with CDC, FDA, and other stakeholders to address them.

9.5 Conclusion

Despite the recommendation of authoritative bodies, such as AAP, FDA and USP, it is evident that some consumers may not be dosing medicines correctly. CHPA supports the outcome of a meeting held at CDC on November 13–14, 2008, to conduct root-cause analysis research to determine the specific circumstances under which parents and other caregivers dose children incorrectly. Results of this analysis will provide direction for educational messages to instruct appropriate consumer behavior. In addition, it was agreed by OTC drug manufacturers to undertake efforts to decrease the variability of standards on volumetric measurements to help parents and other caregivers understand recommended doses and successfully administer medicines to their children with medications would be undertaken.

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Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to FDA Questions

Module 2 of 3

Part 1

Supplemental Data

Module 2 Part 1

1. CHPA Briefing Book for Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee, October 18-19, 2007. Submitted to FDA Docket No. 2007P-0074.

Module 2 Part 2

2. Analysis of Pediatric Nonfatal Reports Coded as Serious from the McNeil Post-marketing Adverse Event Database. CHPA Pediatric Task Force, December 2, 2008
3. Pediatric fatalities associated with over-the-counter (nonprescription) cough and cold medications. Final Report by Rocky Mountain Poison and Drug Center, November 21, 2008
4. Pediatric Safety Data From Clinical Studies on OTC Cough/Cold Medicines. CHPA Pediatric Task Force, December 2, 2008

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

CHPA

founded 1881

ALL CONTENTS AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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CHPA

founded 1881

1. EXECUTIVE SUMMARY

1.1 Introduction

In the August 16, 2007, *Federal Register*, FDA announced a joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee to discuss the safety and efficacy of over-the-counter (OTC) cough and cold medicines marketed for pediatric use. A citizen petition was submitted to the FDA in March 2007 which raised concerns about the safety and efficacy of OTC cough and cold medicines used in children under 6 years of age.

The Consumer Healthcare Products Association (CHPA) is the national trade association representing the leading manufacturers and distributors of OTC medicines and dietary supplements in the United States, including cough and cold medicines. As such, we have an interest and expertise in the subject matter of the Advisory Committee meeting and are providing background information for the committee to review prior to the meeting.

The documents provided in this briefing book address important issues to consider in relation to the safety and efficacy of OTC pediatric cough and cold medicines, including antitussives, expectorants, nasal decongestants, antihistamines, and combination products. CHPA has conducted a review of the available data related to the safety and efficacy of the ingredients available in this category, including market research with caregivers and healthcare professionals who use them. As outlined, the materials included address the following areas:

- The importance and benefits of treatment of cough and cold symptoms
- Efficacy of OTC cough and cold medicines in adults and children
- Overview of pharmacokinetics of cough and cold ingredients
- Safety analyses of published and other public data
- Caregiver and healthcare professional insights
- Recommended action plan
- Our priority is to ensure that parents and families have access to the best possible OTC medicines available today and that caregivers have the resources and information available to use these medications safely and appropriately.

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1.2 Background

OTC cough and cold medicines have been available to consumers and used by parents and physicians for decades. They continue to play an important role in reducing symptoms of the common cold, and it is accepted medical practice to recommend these medicines for symptomatic relief. These medicines do not cure the conditions themselves, but rather provide symptomatic relief for children and adults, as well as lessen the economic burdens caused by colds.

The ingredients under discussion have been available to consumers through the OTC monograph process. Safety, effectiveness, and labeling reviews by experts were conducted on each of these ingredients, resulting in the FDA's assessment of these ingredients as generally recognized as safe and effective. Through the OTC Review, industry and consumers have relied on this regulatory framework for the availability of safe and effective medicines. Over the past few months, however, CHPA and its member companies have conducted our own review of both the safety and efficacy of OTC cough and cold medicines in children ages 0 to under 12 years of age.

1.3 Efficacy

While there are significant data to show the efficacy of these products in adults, several smaller placebo-controlled studies in children did not show significant differences in favor of cough and cold medicines. These results were likely because of the difficulty in evaluating the symptoms of a cold in this young age group. While years of practical application by both doctors and parents using these medicines demonstrates that these ingredients are effective in relieving symptoms of cough and cold in children, it is important to affirm the science supporting these ingredients by conducting additional research under current scientific standards.

Since the OTC monographs were developed for these ingredients, science has evolved that can be brought to bear on the questions before the advisory committee. Investigators now have the practical experience with pediatric research to conduct more comprehensive pharmacokinetic (PK) studies in children between the ages of 2 and 12 years of age. Companies are already

starting to gather important PK data in children, and CHPA and its members are committed to initiating relevant PK studies in key ingredients included in the monograph for OTC cough and cold medicines. Available PK studies in some ingredients confirm the dosing recommendations under the OTC monograph. These further studies should confirm or refine the dosing amounts currently under the OTC monograph.

1.4 Safety

In addition to our efficacy review, CHPA along with outside experts has conducted a review of safety data for OTC cough and cold medicines. This review confirmed that recommended doses of OTC cough and cold medicines are well tolerated in children. Across all age groups, our only safety findings were the known side effects of OTC ingredients, such as drowsiness. The review did reveal rare adverse events, including fatalities that have been reported in association with overdose and misuse of OTC cough and cold medicines. Given the extensive use of these medicines serious adverse events in children of all ages are extremely rare.

Analyses were done for age groups 0 to under 2, 2 to under 6 and 6 to under 12 years of age. Fatal outcomes were most often reported in children less than 2 years of age, either resulting from caregivers administering more than the recommended dose (overdose) or secondary to accidental overdoses following ingestion of these medicines by curious young children who gain accidental and unsupervised access. Data from the American Association of Poison Control Centers shows that in children less than 6 years of age, accidental exposures of OTC cough and cold medicines due to inadequate poison prevention measures result in the highest incidence of overdose, consistent with medications in general. Overdoses from OTC cough and cold medicines resulting in toxicity and requiring healthcare evaluation and treatment are rare.

Data from various sources document that medication errors with OTC cough and cold medicines in children, especially children less than 2 years of age, may lead to overdose. Several high-risk scenarios and behaviors with the administration of these medications to children were identified. These include administering much higher than recommended doses, accidental ingestion,

concomitant use of other medications including prescription drugs, and the misuse of monograph antihistamines for sedation of children.

This review supports the safety of OTC cough and cold medicines when used according to the label as outlined in the OTC monograph. Safety data from prospective clinical trials provides support for performing pharmacokinetic studies in children from 2 to less than 12 years of age.

1.5 Parents and Healthcare Providers

Through research, we know in general that parents understand how to use these medications and feel very comfortable administering them to their children. Most parents consult a healthcare professional before using OTC cough and cold medications, especially in very young children. We also know that pediatricians have the most impact on parents' decisions to give their children OTC cough and cold medicines. While pediatricians, along with other healthcare providers, do recommend using these medications in children 2 years of age and above, they are less likely to recommend OTC cough and cold medications for children less than 2 years of age. Additionally, research shows a lack of understanding among caregivers about the active ingredients.

1.6 Recommendations

Based on the data, findings, and analyses presented in this book, CHPA and its member companies are taking the following steps to encourage the appropriate use of all of these medicines:

- We recommend that the label be changed in all OTC cough and cold medicines to read "Do Not Use" in children 0 to under 2 years of age.
- We recommend that additional language be added to the label of antihistamines currently under the OTC monograph to indicate "Do not use to sedate children."
- We are committed to supporting a national education campaign targeted at caregivers and healthcare professionals to raise awareness of these label changes and reinforce the safe use of these medicines in all appropriate age groups.
- We are committed to conducting a prospective safety study.

- We are committed to conducting pharmacokinetic studies of all relevant ingredients in children 2 to under 12 years of age where additional data is needed.
- We are committed to working in close cooperation with FDA and other experts to identify strategies to bridge efficacy data, including the development of validated, pediatric pharmacodynamic or clinical symptom endpoints.

CHPA and its member companies have a long history of educating consumers on the safe use of OTC medicines and have taken the lead on many important initiatives over the years. From child resistant packaging to tamper-evident packaging and the development of the OTC Drug Facts label in conjunction with FDA, CHPA has been proactive and unwavering in its commitment to providing the highest quality medicines to the millions of American families who rely on them each and every day, as well as the information and tools to use these medicines appropriately. We see the recommendations and initiatives outlined in this document as a continuation of this long standing commitment.

The materials provided in this document reflect the collective work and views of the following CHPA member companies who currently market OTC cough and cold medicines for children:

- Adams Respiratory Therapeutics
- McNeil Consumer Healthcare
- Novartis Consumer Health, Inc.
- Perrigo Company
- Prestige Brands Holdings, Inc.
- The Procter & Gamble Company
- Wyeth Consumer Healthcare

2 THE IMPORTANCE OF TREATMENT OF COMMON COLD SYMPTOMS

2.1 Key Points

- Symptomatic treatment of the common cold is well accepted medical practice in adults and children
- There are significant economic burdens due to colds
- While there is limited efficacy data from clinical trials, survey data suggest that both healthcare professionals and parents believe that OTC cough and cold medicines are beneficial in the symptomatic management of colds.

2.2 Symptomatic Relief

The common cold is recognized as the most common infectious syndrome of humans [Eccles 2005, Gwaltney 2002] with adults experiencing 2 to 4 symptomatic infections each year and children experiencing 6 to 8 [Heikkinen and Jarvinen 2003]. Symptomatic treatment of the common cold in adults and children has long been established as acceptable medical practice because there is no effective preventive measure or treatment available for the underlying viral etiology [Turner 2001]. Consequently, medical intervention is limited to the symptom relief and reduction of associated morbidity, facilitating the return to normal function while the condition resolves naturally. For the vast majority of uncomplicated cold episodes in adults and children, management of symptoms with OTC cough and cold medicines (antitussives, nasal decongestants, antihistamines, and expectorants) helps to achieve this objective.

2.3 Prevalence and Pattern of Cold Symptoms in Children and Adults

In the United States, cough is the most frequent complaint for which patients seek medical attention, and nasal congestion is mentioned in the top 20 reasons for a doctor's office visit [Woodall 2004]. Both cough and nasal congestion are symptoms frequently associated with the common cold.

Children of all ages, as well as adults, experience nasal symptoms (e.g. congestion and rhinorrhea) and cough as a result of the common cold. However, the prevalence and pattern of symptoms vary with age. In a longitudinal prospective study that enrolled infants from birth until one year of age with acute respiratory infections, 96% of the 984 infants had a runny/obstructed nose (rhinorrhea and nasal congestion) and 76.8% had a cough [Kusel

2006]. Table 2.1 summarizes the symptoms reported by parents or guardians in this study. Similar to adults, the infants experienced nasal symptoms and cough. However, unlike adults, at least one third of the infants also experienced a rattly or wheezy chest.

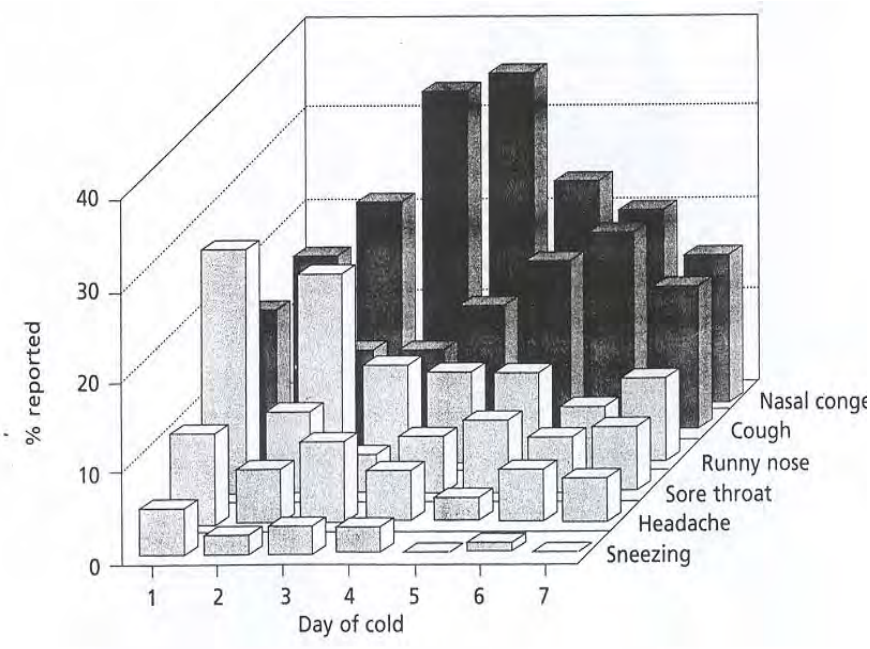
Table 2.1 Symptoms From 984 Episodes of Acute Respiratory Infections in Infants from Birth to 12 Months of Age

Symptom	Number (%)
Runny/obstructed nose	945 (96.0)
Cough	756 (76.8)
Rattly or wheezy chest	329 (33.4)
Fever	238 (24.2)
Wheeze present	95 (9.7)

A recent study examined cold symptoms in 81 predominantly school-aged children, ranging from 2 through 12 years. Symptom diaries on the children were kept for 10 days following onset of a cold. The most common reported symptoms at their maximum prevalence over 10 days were nasal congestion (88%), runny nose (72%), cough (69%), and sneezing (55%) [Pappas in press]. Fever and headache were each reported in 15% of children at onset of the cold.

Research in naturally acquired and artificially induced colds confirms that the symptoms tend to occur in a predictable pattern over the 7 to 10 days of a typical uncomplicated infection (Figure 2.1) [Gwaltney 2002, Tyrrell 1993, Gwaltney 1967, Witek 1992].

Figure 2.1 The clinical course of acute upper respiratory tract infection [adapted from Witek 1992]



In addition, epidemiological research in over 1,000 common cold patients by the Bristol Myers Company confirmed that over the period of a normal, uncomplicated infection, 32-52% of patients had as many as 4 of the key signs and symptoms of the common cold simultaneously (Table 2.2) [Bristol Myers Company Petition to US FDA 1979].

Table 2.2 Multiple symptoms occurring simultaneously during the common cold [Bristol Myers Company Petition to US FDA 1979]

Day of Illness	% of patients with 4 symptoms
1	32.31
2	44.25
3	51.06
4	47.76
5	49.06
6	52.63
7	38.89
8 or more	49.18

These data, and those of Gwaltney in naturally acquired colds, coupled with the results of Tyrrell and Turner from induced colds, emphasize the medical desirability for treatment of multiple symptoms [Gwaltney 1967, Tyrrell 1993, Turner 1996]. Additionally, the effects of these symptoms are often most bothersome to patients in the evening, particularly as they retire to bed, and can affect rest, and subsequent performance the following day [Drake 2000]. Similarly, in school-aged children, it has been shown that multiple coincident symptoms are part of the cold, in particular nasal symptoms and cough [Pappas in press]. Based on the range of symptoms experienced by patients and the coincidence of multiple symptoms, it is reasonable to have OTC combination cough and cold medicines that can relieve symptoms of cough, nasal congestion, and rhinorrhea.

2.4 Economic Burden of Colds

Morbidity associated with the common cold is known to have a considerable social cost. In the United States, the magnitude of the economic impact has been estimated at $25 billion lost due to non-influenza common cold, of which $16.6 billion is lost on-the-job productivity, $8 billion due to direct employee absenteeism, and $230 million due to caregiver

absenteeism [Bramley 2003, Fendrick 2003]. It seems reasonable to suggest that much of this cost is due to care for children, as the common cold is the most prevalent childhood illness, and it occurs with greater frequency in children compared to adults. Adults typically experience 2 to 4 symptomatic infections each year and children experience 6 to 8 [Heikkinen and Jarvinen 2003].

Among children, there is absenteeism from school due to the common cold estimated at 189 million school days annually and increased healthcare provider interaction [Fendrick 2003]. Lack or reduction of availability of symptomatic cough and cold preparations would considerably impact the healthcare system in the form of additional physician visits in a search of symptom resolution, and potentially an increase in unnecessary and inappropriate antibiotic prescribing since many children with colds are given prescriptions for antibiotics [Nyquist 1998]. Inappropriate use of antibiotics would provide minimal therapeutic benefit, add substantially to healthcare costs, and raise antibiotic resistance concerns [Steinman 2003].

Economic data on the impact of OTC cough and cold medicines is limited but suggests that these products lessen the economic burden associated with colds. Temin suggested that the availability of OTC cough and cold medicines contributed to an average reduction in physician visits in the U.S. by 110,000 per year over a 14 year period from 1976 to 1989 [Temin 1992]. In terms of medical costs of physician visits and costs of prescription drugs, another study estimated that OTC cough and cold medicines save consumers $3 billion per year [Kline 1997].

2.5 Exposure Estimates

Using information and estimates from household panel data provided by Information Resources, Inc., we estimate that there were approximately 288 million units of pediatric cough and cold products sold in the last 3 years ending December 31, 2006. This translates into approximately 95 million units sold annually. An estimated 39% of households purchase these products in this period, meaning there were a projected 44 million buyers.

2.6 Benefits to Children and Parents

There are data from controlled clinical trials evaluating efficacy of OTC cough and cold medicines in the pediatric population (see Section 3, Efficacy). It should be noted that the small sample size and inconsistent endpoints in these trials can make them difficult to

interpret. However, the benefits of OTC cough and cold medicines to the pediatric population have been demonstrated in survey studies of both healthcare providers and caregivers.

In 2007, CHPA commissioned a national survey of 3000 Americans on their use of OTC products to treat cough symptoms resulting from the flu, cold, or other respiratory ailments [CHPA 2007a]. In 648 households that had children age 18 and under, 73% of parents and caregivers indicated that they administered an over-the-counter cough medicine to the child in their home who was experiencing a cough, regardless of the age of the child. A total of 91% of parents and caregivers reported that use of OTC cough remedies helped them or the child feel more comfortable. Importantly, 89% of adults, parents, and caregivers indicated that the cough remedies they used effectively helped them or the child in their household cough less. More than three-quarters of adults, parents and caregivers also indicated that cough remedies helped them and the child both function and sleep better.

Another recent survey was conducted among 1,000 adults living in the United States, and a stand-alone survey of 150 adults with children ages 12 and under in the home, to assess common practices among adults who have children experiencing nasal congestion [CHPA 2007b]. When adult Americans were asked about common practices used when a child living in their home experiences nasal congestion, the most commonly reported action was giving the child an OTC medication. In total, 70% of respondents reported using an OTC medication to treat nasal congestion. This practice appears to be the most common practice across all age groups, genders, and regions of the country.

The second most commonly reported practice in treating a child with nasal congestion is talking to a doctor (32%). This practice is most prevalent in the South, where 50% report talking to a doctor when their child is experiencing nasal congestion.

Table 2.3 indicates the level of agreement with each of the 4 statements included in the CHPA study. Please note that the percentages add to more than 100%, as this question allowed more than one response.

Table 2.3 Survey Results - What Most Americans Do to Treat a Child with Nasal Congestion

	Total Agree
Use an OTC medicine, that is, a medicine that you can buy without a prescription	70%
Talk to a doctor	32%
Use a prescription medicine	24%
Wait or do nothing	18%

Only 3% of respondents who administered an OTC medication to treat nasal congestion reported that the medication had no positive effect on the child. The remaining 97% report at least one positive benefit (Table 2.4). These include helping the child feel more comfortable, breathe easier, function better and relieve a runny nose. As seen in the table (Table 2.4), 8 in 10 (81%) reported that an OTC medication helped their child feel more comfortable. These benefits are widely reported across all segments of the population.

Table 2.4 Survey Results – What Caregivers Believe are the Benefits of OTC Decongestants

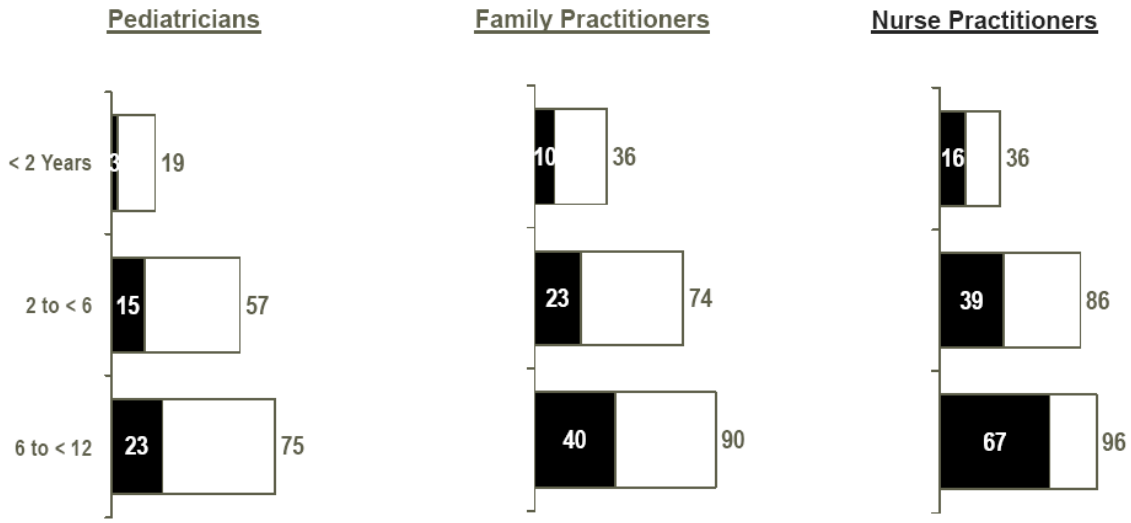
	Total Agree
It helped them feel more comfortable	81%
It helped them breathe more easily	72%
It made their nose less runny	69%
It helped them function better	60%
None of the above/No effects	3%

These findings show that the majority of adult Americans turn to OTC medications as a first response when a child in the home is experiencing nasal congestion. There is also common belief that these medications offer multiple benefits for the child.

Likewise, a recent survey of 310 healthcare professionals including pediatricians, family practitioners, and nurse practitioners was conducted by Wyeth to obtain their opinions on the use of OTC cough and cold medicines, specifically, antihistamines, decongestants, antitussives, and expectorants, in three pediatric age groups: under 2 years, 2 to under 6 years and 6 to under 12 years [Wyeth 2007]. In general, the results of the survey indicated that:

- The majority of healthcare practitioners including pediatricians are in favor of recommending OTC cough and cold medicines for their pediatric patients in the 2 to under 6 and 6 to under 12 year age groups (see Figure 2.2).
- The top 4 symptoms that triggered medical professionals to recommend the use of an OTC cough and cold product were: fever, cough, stuffy nose, and difficulty sleeping.

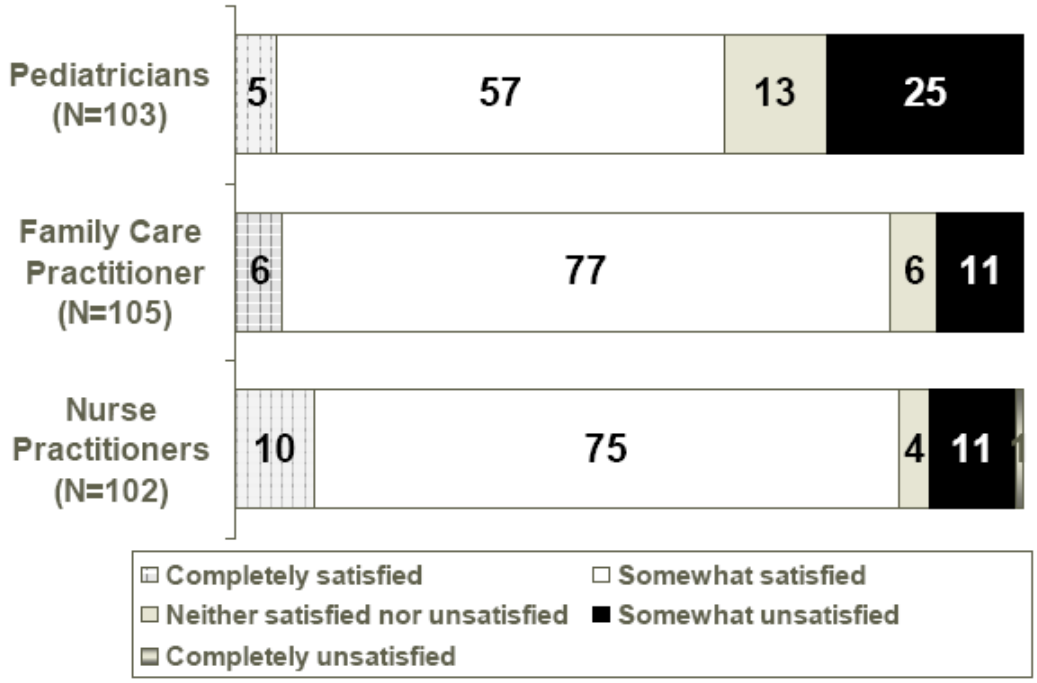
Figure 2.2 Healthcare Professional Opinions on the use of OTC Products to Treat Cough and Colds by Age Group



Numbers in the blackened areas reflect the percent of healthcare professionals (by discipline) that were very favorable towards OTC cough and cold medicines. The open area reflects the proportion of healthcare professionals that were somewhat favorable. The total percent of healthcare professionals that were very favorable or somewhat favorable is indicated at the end of each bar.

The survey also found that the age of the child and symptom severity are 2 key drivers that influence the recommendations of OTC cough and cold medicines by medical professionals. The majority of medical professionals cited a specific dose when OTC cough and cold medicines were recommended. Overall, the majority of healthcare professionals perceived that parents are at least somewhat satisfied with the effectiveness of their recommended OTC cough and cold medicines (Figure 2.3). Furthermore, medical professionals believe that the major benefits of OTC cough and cold medicines are symptom relief and allowing the child to get a good night of sleep.

Figure 2.3 Healthcare Professionals Perception about Parent Satisfaction with Recommended OTC Cough and Cold Medications for their Children (%)



When questioned about what they would recommend if pediatric OTC cough and cold medicines were no longer available, most medical professionals would recommend a home therapy (e.g. humidifier, normal saline nose drops). They also indicated that prescription drugs would be more common and that proper dosages of adult medications would be an option for older children.

In summary, these data suggest that healthcare practitioners and parents believe that OTC cough and cold medicines do provide benefit to the pediatric population. In contrast to the view of a recently submitted Citizen Petition [Sharfstein 2007], the results from this healthcare practitioner survey suggest that there is no consensus among physicians that OTC cough and cold medicines should be restricted for use in the 2 to under 6 year age group, and that, in fact, only a minority of them favored the use of the products for the 0 to under 2 year old group. Given the 95 million units of pediatric OTC cough and cold medicines sold annually and the long history of safe use with these products at recommended doses, it is more than reasonable to conclude that consumers derive some benefit from them.

3 EFFICACY OF OTC COUGH AND COLD MEDICINES

3.1 Key Points

- Evidence for the efficacy and safety of OTC cough and cold medicines based on randomized, placebo-controlled trials in adults are prevalent in the literature.
- The results of pediatric studies of OTC cough and cold medicines have been inconclusive to date.
    - There are considerable challenges and limitations to the study of cough and cold medicines in pediatrics related to study design and lack of sensitive relevant endpoints.
    - The majority of pediatric randomized, controlled trials (RCTs) have been underpowered.
    - Recommendations by professional, authoritative bodies to not use certain ingredients in young children relate, for the most part, to the lack of robust clinical trial data in this patient population.
- CHPA concludes that it would be beneficial to expand the body of evidence for the use of cough and cold medicines in children.
    - Studies must be appropriately powered to achieve statistical significance.
    - Appropriate efficacy endpoints based on the mechanism of action (MOA) of the test medications must be employed.
    - The field will be advanced by the development of robust, validated methodology for evaluating the signs and symptoms of the common cold.

3.2 Introduction

In the Citizen Petition, Docket # 2007P-0074, Sharfstein *et al* contend that OTC pediatric cough and cold medications are *not* generally recognized as safe and effective (GRASE). CHPA disagrees with this assessment, and this section reviews the efficacy results upon which this opinion is based.

There are a number of drug classes employed in the symptomatic treatment of the common cold. Each class of drugs exerts a particular mechanism of action or symptom-specific effect, and for some classes there is more than one compound available. Several OTC cough and cold products were approved under a New Drug Application (NDA), and the remainder of ingredients are addressed in the “Cold, Cough, Allergy, Bronchodilator, and

Antiasthmatic Drug Products for Over-the-Counter Human Use" monograph 21 CFR 341. Products approved under an NDA demonstrated efficacy and safety as determined by rigorous review prior to approval by FDA. Further, monograph ingredients underwent a structured review process to achieve inclusion in the monograph. The basis for the OTC monograph for these ingredients is that they are GRASE (Category I = generally recognized as safe and effective for its intended use). Cough and cold medications are available as monotherapy and in various combination products as permitted by the respective NDA or monograph. Recommended dosing is provided in these documents.

Clinical studies have established safe doses for adults. There are a number of positive efficacy studies for each medication in adults. Yet, evaluating the effectiveness of cough and cold medications is challenging. The lack of sensitive, specific, and validated methodology to evaluate common cold symptoms; the magnitude of the placebo effect; and the subjective nature of many of the symptoms has resulted in inconsistent results across adult trials and confounded the conduct and interpretation of pediatric clinical trials.

At present, there is a lack of robust efficacy data for cough and cold medicines in children. However, pediatric research networks have expanded, and study methodology and pharmacologic knowledge have evolved. Therefore, it may now be possible to effectively readdress the study of these products in children. Such studies would provide additional population pharmacokinetic data which underlay safe and effective dosing with these products. An industry proposal for a clinical trial program is included in this document (Section 7).

For the purposes of our analysis of safety and efficacy of OTC pediatric cough and cold ingredients, we focused on the most prevalent ingredients, as listed below:

Therapeutic Category	Active Ingredients	Sample Indications
Nasal Decongestants	Pseudoephedrine HCl Phenylephrine HCl	Temporarily relieves • nasal and sinus congestion • stuffy nose • clogged up nose .
Antihistamines	Chlorpheniramine Maleate Diphenhydramine HCl Brompheniramine Maleate Doxylamine Succinate	Temporarily (relieves, alleviates, decreases, or reduces) these cold symptoms: • runny nose • sneezing
Antitussives	Dextromethorphan HBr Diphenhydramine HCl	Temporarily helps • you cough less • to suppress the impulse to cough • reduce the cough reflex that causes coughing • decrease the intensity of coughing
Expectorants	Guafenisin	Temporarily helps • loosen phlegm and bronchiole secretions •makes cough more productive

3.3 Efficacy Data

3.3.1 Adult Efficacy Data

There are a number of randomized, double blind, placebo-controlled studies of cough and cold therapies in adults, many of which demonstrated statistically and clinically significant improvements in symptoms, and some of which may have been considered as a basis of support for the OTC monograph. Described in this section are published, randomized, double blind, placebo-controlled studies in adults that evaluated cough and cold medications, which overall suggest that adults do accrue significant benefit from these drugs. Reviews by independent committees (Cochrane Library, The American College of Chest Physicians, The European Respiratory Society, The American Academy of Pediatrics) of each drug class or of this therapeutic area, are presented where they exist. Listings of published placebo-controlled randomized clinical trials (RCTs) by drug, by age (adult and pediatric) along with study designs, sample sizes, and results are found in Appendix 1 of this document.

3.3.1.1 Effect of antihistamines on nasal symptoms associated with the common cold

A meta-analysis of 9 studies by D'Agostino summarized the efficacy of antihistamines (chlorpheniramine (n=202), doxylamine (n=307) and placebo (n=518)) in reducing the severity of runny nose and sneezing, and concluded that, "Antihistamines are statistically significantly more effective than placebo in reducing the severity of runny nose and sneezing associated with the common cold. Most importantly, the differences between antihistamines and placebo were clinically relevant based on the goal of therapy criteria established a priori. The benefits of antihistamine therapy in the common cold appear to be clinically achievable." The goal of therapy, predefined by the authors as a 50% reduction in the mean symptom score, was significantly better for antihistamines (vs placebo) for both sneezing and runny nose, indicating that the observed treatment effects were clinically, as well as statistically, significant. [D'Agostino 1998].

In the literature, RCTs of antihistamine monotherapy in adults with the common cold are positive overall. Of the 6 studies identified, 4 showed efficacy in control of various cold symptoms. The other 2 studies did not demonstrate efficacy:

- Howard studied chlorpheniramine (CHLOR) 4 mg 4 times daily for 6 days in subjects with signs and symptoms of the common cold, using subjects' subjective assessments of symptoms and physician assessments. CHLOR (n=133) was superior to placebo (n=138) in lessening the degree of symptoms, with statistically significant differences in the subjects' overall evaluation favoring CHLOR on the first day (27.1% vs 18.8%) and as late as the seventh day (71.4% vs 63.8%). Other measures trended in favor of CHLOR [Howard 1979].

- Crutcher and Kantner studied adults within 48 hours of onset of cold symptoms. They were given CHLOR 4 mg (n=52) or placebo (n=54) 4 times daily for 7 days. Subjective evaluation of symptoms by subjects and of signs by physicians showed significant relief in cold symptoms and a clear trend toward reduction of signs of a cold [Crutcher 1981].

- Doyle gave CHLOR 4 mg (n=19) or placebo (n=18) every 4 hours for 5 days to subjects with rhinovirus-induced colds. Objective assessments of nasal patency (by rhinometry), eustachian tube function (by 9-step test and sonotubometry), middle ear pressure (by tympanometry), and nasal clearance (by dyed-saccharin technique), and quantification of nasal secretions and evaluations of symptoms by subjects, demonstrated CHLOR to be effective in decreasing sneezing and in increasing mucociliary clearance [Doyle 1988].

- Gaffey studied CHLOR 4 mg (n=10) vs placebo (n=11) 4 times daily for 4 days in subjects who were intranasally inoculated with rhinovirus, measuring expelled nasal mucus weight and used nasal tissue counts, with monitoring of clinical symptoms to determine frequency and severity of clinical illness. CHLOR was not found to have a significant effect on nasal symptoms or mucus production [Gaffey 1987].

- Gwaltney and Druce induced colds and administered brompheniramine (BROM) 12 mg (n=113) or placebo (n=112) twice daily, obtaining weight of nasal secretions and subjective symptom scores. Mean nasal secretion rates for BROM were significantly lower vs placebo on all treatment days. Similar results were seen with subjective symptom scores including rhinorrhea, sneezing counts, and sneezing severity [Gwaltney 1997].

- Eccles studied doxylamine (DOX) 7.5 mg (n=345) vs placebo (n=343) 4 times daily for 9 doses in subjects with colds, evaluating day 2 subjective assessment of runny nose and sneezing, and nasal secretion rates. There were statistically significant differences favoring DOX for sneezing and runny nose on days 2 to 3, and days 1 to 3, respectively. Outcome for nasal secretions were not reported [Eccles 1995].

The Cochrane Review of antihistamines (AH) for the common cold included 32 papers that had 35 comparisons; 22 trials studied AH monotherapy and 13 trials studied combinations of AH with other medications. A total of 8930 patients were involved. The conclusion was that antihistamines alone are not an effective treatment for the common cold, but might have a small effect in combination with decongestants. Combinations of antihistamines with decongestants were not effective in small children based on this review. In older children and adults, most trials show a beneficial effect on general recovery as well as on nasal symptoms.

3.3.1.2 Decongestants

Five placebo-controlled randomized studies of pseudoephedrine (PSE) as monotherapy (one study also included a PSE with ibuprofen arm), and one placebo-controlled study using PSE with aspirin, and PSE with paracetamol (acetaminophen), found PSE effective in reducing symptoms of nasal congestion. No negative placebo-controlled RCT of PSE was identified. Although the efficacy of phenylephrine (PE) 10 mg has recently been questioned, a recent meta-analysis by Kollar demonstrated that PE 10 mg produces a significant improvement in nasal airway resistance.

Bye compared PSE 60 mg alone (n=61) and in combination with triprolidine 2.5 mg (n=55) vs placebo (n=60) in adults with the common cold. Sneezing, nasal obstruction, and overall responses to treatment were significantly improved with PSE and PSE with triprolidine compared with placebo [Bye 1980].

Sperber compared PSE 60 mg alone (n=23) and in combination with ibuprofen 200 mg (n=23) vs placebo (n=10) in young adults intranasally inoculated with rhinovirus 30 hours before initiating treatment. Total symptom scores compared to placebo were reduced by 59% with the combination and by 48% with PSE alone, but only nasal symptom scores were substantially different between the groups; there was significantly less rhinorrhea (nasal secretion weight) vs placebo in both PSE treatment groups (41% for PSE and 30% for the combination vs placebo); nasal patency was most improved with the combination [Sperber 1989].

Taverner compared single-dose PSE 60 mg (n=25) with placebo (n=27) in subjects with the common cold (<5 days of symptoms) and moderate-to-severe nasal congestion. Objective measurement of nasal cross-sectional area and volume by acoustic rhinometry, demonstrated significant increases with PSE in total nasal minimum cross-sectional area (AUC increased 7% over placebo) and nasal volume (AUC increased 11% over placebo) [Taverner 1999].

Eccles studied PSE 60 mg (n=119) and placebo (n=119) 4 times daily in subjects with moderate nasal congestion associated with the common cold (onset <72 hours). Objective measurement of nasal airway resistance by posterior rhinometry and objective scoring (VAS) of nasal congestion every hour for 4 hours after first dose on day 1 and after the last dose on day 3 revealed significantly decreased nasal airway resistance 2 to 4 hours after first dose of PSE on day 1, and 0 to 4

hours after last dose on day 3 (percent reduction in geometric mean relative to placebo, 10.4% to 20.5%); lower subjective congestion scores were statistically significant after one dose of PSE on day 1, but not after multiple doses on day 3 [Eccles 2005].

Latte compared PSE 60 mg to placebo (total n=216) administered 4 times daily for 3 to 4 days using objective measurement of nasal airway resistance by posterior rhinometry and objective scoring of symptom severity using a VAS. They found decreased nasal airway resistance and improved symptoms of congestion with PSE [Latte 2006].

Loose evaluated PSE 60 mg with aspirin 1000 mg (n=161) vs placebo (n=162) in subjects with nasal congestion associated with common cold, as well as comparisons of the combinations, PSE 30 mg with aspirin 500 mg (n=161) vs PSE 60 mg with paracetamol (acetaminophen) 1000 mg (n=159). They employed subjects' subjective assessments of nasal congestion, with primary efficacy variable being the area under the curve (AUC) for differences from baseline on a nasal congestion scale in first 2 hours after treatment. All active treatments were statistically superior to placebo. PSE 60 mg with aspirin was efficacious for all subjects for the entire 6 hours, with significant results for nasal congestion and relief of nasal stuffiness [Loose 2004].

Cohen compared single doses of phenylephrine (PE) 10 mg, 15 mg, and 25 mg, and placebo in 48 subjects with nasal congestion associated with the common cold, using objective determination of nasal air flow/resistance by electronic posterior rhinometry and subjects' subjective estimations of nasal congestion. Results included decreased nasal flow/resistance with all three doses of PE tested, apparent at 15 minutes, maximal between 30 and 90 minutes, and still present 120 minutes after treatment. (Although not described by the authors, the figures indicate that the differences for all three doses were approximately 20% to 50% greater than for placebo, for both nasal flow and nasal symptom scores) [Cohen 1972].

Kollar performed a meta-analysis of the efficacy of a single dose of phenylephrine (PE) 10 mg compared to placebo in adults with acute nasal congestion due to the common cold. Seven cross-over studies (n=113) and a reanalysis of a parallel group study (n=25 in both verum and placebo group) support the effectiveness of a single oral dose of PE 10 mg as a decongestant in adults with acute nasal

congestion associated with the common cold. Nasal airway resistance (NAR) was measured in these studies. The mean reduction from baseline in NAR was approximately ⅔ to 2 times greater for phenylephrine than for placebo between 15 and 90 minutes after dosing [Kollar 2007].

There were no studies in children meeting the criteria for inclusion in the Cochrane Review of nasal decongestants. Seven adult studies were included (one of which studied an intranasal decongestant, n=106; the others were oral decongestant studies n= 630) and it was concluded that nasal decongestants offer a modest improvement in nasal congestion supported by a significant decrease in measured nasal airways resistance. Adverse effects on treatment were no more likely than with placebo, and the most common adverse effect on treatment was insomnia (5%). The authors concluded, “There is insufficient data on the use of these medications in children and therefore they are not recommended for use in children younger than 12 years of age with the common cold.”

3.3.1.3 Antitussives

A review of the literature found 3 randomized placebo-controlled trials of dextromethorphan (DXM) and a meta-analysis of 6 other DXM RCTs in the treatment of cough associated with the common cold. Although one trial was negative, the other trials found DXM efficacious and well-tolerated in the treatment of acute cough associated with colds, reducing cough counts, latency between coughing bouts, and cough effort.

Tukiainen studied DXM 30 mg (n=36) and DXM 30 mg with salbutamol 2 mg (n=38) vs placebo (n=34) in outpatients who had an acute respiratory infection with cough,

using subjects' subjective scoring of daytime cough frequency and severity and nighttime cough severity and breathlessness, objective measurement of sputum quantity and subjective assessment of ease of expectoration. The results indicate DXM with salbutamol was more effective than the other two groups in suppressing nighttime cough. A significant improvement in symptom parameters was seen during the day for all treatment groups, and there were no significant differences between groups in symptom score for cough frequency or severity during the day, sputum quantity or ease of expectoration [Tukiainen 1986].

Parvez conducted 3 double-blind randomized placebo-controlled trials (n=108; n=134; n=209; total n=451) of a single dose of DXM 30 mg for acute cough due to acute upper respiratory infection. Objective quantitative evaluation with a multidimensional cough measurement system (recordings), and subjective patient assessments of cough and rating of troublesomeness of cough, consistently showed significantly reduced cough counts and total effort, with increased rest periods and unchanged average intensity per cough bout. Subjective assessments with VAS in 2 studies showed no treatment effects, but in the third study global assessment of cough showed a trend towards improvement with DXM at 120 minutes and the rating of cough troublesomeness showed DXM significantly superior at 120 minutes [Parvez 1996].

Lee studied DXM 30 mg (n=21) vs placebo (n=22) as a single dose for acute cough associated with URI, using objective recording of cough frequency (CF) and cough sound pressure level (CSPL), along with subjective patient assessments of cough severity. There was no significant difference from placebo for CF, CSPL and subjective scores. There was a statistically significant greater reduction in mean CSPL from baseline to 90 minutes with DXM, but not at 135 or 180 minutes [Lee 2000].

Pavesi performed a meta-analysis of 6 RCTs using a single 30 mg dose of DXM (n=356) or placebo (n=354) for acute cough due to uncomplicated URI, using objective recording continuously for 3 hours after treatment, measuring cough bouts, cough components, cough effort, cough intensity, and cough latency. The meta-analysis showed consistent results across most of the studies for each of the efficacy variables, with statistically significantly greater reductions vs placebo in

cough bouts (-12.7%), cough components (-13.4%), cough effort (-17.3%), and increase in cough latency (+17.3%) with DXM, but not for cough intensity (-5.8%) [Pavesi 2001].

3.3.1.4 Expectorants

A review of the literature found 3 RCTs of guaifenesin as a treatment of common cold symptoms in adults. One studied guaifenesin for cough, and this study was negative. The others evaluated guaifenesin as an expectorant, and it was found to be effective, thinning sputum and decreasing sputum volume, as well as decreasing cough frequency and intensity.

Robinson studied adults with moderate-to-severe cough associated with URI, treated with guaifenesin (GUA) 200 mg (n=118) or placebo (n=121) 4 times daily for 3 days. Subjective ratings by subjects and physician evaluation, along with objective measure of sputum characteristics found GUA significantly reduced cough frequency, cough intensity, and chest discomfort in subjects with initial nonproductive and productive cough and significantly increased sputum volume and facilitated raising sputum in subjects with initial productive cough [Robinson 1977].

Kuhn administered GUA 400 mg (n=33) or placebo (n=32) every 6 hours for 30 hours in subjects with cough associated with acute respiratory illness of < 48 hours duration. Using objective recorded cough counting and subjects' subjective ratings of cough, cough severity, cough discomfort, chest discomfort, sputum quantity, and thickness, the study revealed no antitussive effect, but GUA was associated with a perceived decrease in sputum quantity and a reduction in sputum thickness [Kuhn 1982].

Parvez compared GUA 1200 mg/day (n=31) to placebo (n=29) over 14 days in adult patients with chronic cough. GUA-treated patients maintained a steady sputum volume output over the study period with a significant difference to placebo of 37% on day 14. Fucose, a marker for sputum glycoprotein, was significantly reduced in the GUA compared to the placebo group on day 14. On a subjective scale for ease of expectoration, a subgroup of high sputum producers (>40mL pre-treatment) reported a large and significant improvement. GUA also produced

larger reductions in average intensity per cough compared to placebo on days 4 and 7 which was statistically significant on day 4 ($p<0.05$) [Parvez 1996].

3.3.1.5 Drug combinations

Seven published, randomized placebo-controlled trials of various combinations of AH/decongestant with or without DXM as multisymptom cold relievers were identified, and each study found efficacy vs placebo:

Berkowitz study of PSE 120 mg with loratadine 5 mg (n=142) vs placebo (n=141) in subjects with the common cold used physician assessment of overall response and evaluation of severity scores for rhinorrhea, nasal patency, and swelling on days 3 and 5, as well as subjects' subjective scoring of overall response and symptoms. Evaluations by both subjects and physicians suggest the PSE-loratadine combination is superior to placebo in relieving symptoms, including nasal congestion, sneezing, postnasal drainage (PND), and nasal discharge [Berkowitz 1989].

Blanco de la Mora compared 2 tablets of (PSE 60 mg with loratadine 2.5 mg and acetaminophen 500 mg) with placebo (total n=40) using investigator subjective assessment of nasal congestion, rhinorrhea, and general malaise on days 3 and 5, as well as subjects' subjective evaluation of symptoms. Significant difference between treatment groups was observed on day 3, and a favorable effect on edema of nasal mucosa and significant reduction of rhinorrhea were found on day 3 [Blanco de la Mora 2000].

Curley evaluated PSE 120 mg with dexbrompheniramine 6 mg (n=38) vs placebo (n=35) twice daily for 7 days in adults with common cold symptoms (present for 12 to 72 hours). Objective pulmonary function testing, and subjects' subjective daily assessments of severity of 17 symptoms for 14 days demonstrated reduced post-nasal drainage (PND) and significantly decreased severity of cough, nasal discharge, and throat clearing during first few days of treatment. Cough was 20 to 30% less prevalent in the active group than in the placebo group within 3 days of starting therapy. Active therapy demonstrated significantly lower mean severity rank of cough on days 3 to 5, of nasal discharge on day 2, of nasal obstruction on days 2 to 5 and of throat clearing on days 2 to 3 [Curley 1988].

Thackray used a double blind cross-over design with 70 subjects taking placebo vs a combination of DEX 15 mg with DOX 7.5 mg and ephedrine 8 mg and acetaminophen 600 mg, given in a single bedtime dose on 2 consecutive nights in subjects with the common cold. Subjects' subjective assessments of symptoms indicated cough improved significantly vs placebo, as did nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, and disturbed sleep. A significant number of active treatment subjects experienced global symptomatic relief compared with subjects on placebo [Thackray 1978].

Mizoguchi studied DEX 15 mg with DOX 7.5 mg and acetaminophen 600 mg and ephedrine 8 mg (n=224) vs placebo (n=208) in a single evening dose in subjects with common cold symptoms for 1 to 5 days who were experiencing at least moderate nasal congestion and runny nose, at least a mild cough, and at least mild pain with one or more of the following: sore throat, sore chest, headache, or body aches and pain. Subjects' subjective scoring of symptoms 3 hours post-dosing and 1 hour after rising the next morning found clinically and statistically significant relief vs placebo for the primary endpoint (composite of nasal congestion/runny nose/cough/pain relief scores 3 hours post-dosing). Each individual symptom score was also significantly improved at 3 hours, and there were clinically and statistically significant improvements on composite score and each individual symptom score the following morning [Mizoguchi 2007].

Galvez studied the common cold with associated cough, nasal congestion, and rhinorrhea, using DEX 20 mg with PSE 60 mg and azatadine 1 mg (n=28) or placebo (n=32) 3 times daily for 5 days. Subjective assessment of symptoms by a physician in consultation with subjects found more rapid and complete relief of nasal congestion and cough, excellent or good therapeutic response to treatment at interim and final evaluations in statistically greater number of subjects on active treatment, as well as faster onset of symptomatic relief (reported at 12 hours by 55% of treated vs 17% of placebo subjects; excellent or good overall therapeutic responses by day 3 in 60% of treated vs 8% of placebo group; and by day 5 in 77% of treated vs 21% placebo subjects [Galvez 1985].

Scavino gave DEX 20 mg with PSE 60 mg and azatadine 1 mg (n=29) or placebo (n=29) 3 times daily for 5 days to subjects with the common cold and associated cough. Physician assessment of signs and subjective assessment of symptoms (in consultation with subjects) revealed statistically significant greater reduction in

symptom severity scores at interim and final evaluations with treatment (59% improvement vs 33% on placebo at day 3; and 92% vs 69% on day 5), as well as faster onset of symptomatic relief (reported at 12 hours or less by 40% of treated subjects vs none on placebo); and more rapid improvement (lessened severity) in signs on treatment, a statistically significant difference (57% improvement vs 30% with placebo on day 3, and 93% vs 73% on day 5). Excellent or good overall therapeutic responses by day 3 for 76% of treated vs 17% of placebo group, and by day 5, 88% of treated vs 48% of placebo group [Scavino 1985].

The Cochrane Review of OTC medications for acute cough in adults and children evaluated the effect on cough of several classes of medications used to treat cough and cold. The review encompassed 24 RCTs (17 in adults and 7 in children) involving 2,876 adults and 516 children. Antitussives, expectorants, mucolytics, antihistamine/decongestant combinations and other drug combinations were evaluated. It was concluded that there is no good evidence for or against the effectiveness of OTC medicines in acute cough. Interestingly, the authors state that the results of their review have to be interpreted with caution due to differences in study designs, populations, interventions and outcomes between studies. The numbers of studies in each group were small, and studies often showed conflicting results. They concluded that the effect sizes in many studies were unclear, and questioned whether all of the positive results are clinically relevant.

The European Respiratory Society (ERS) guidelines on the assessment of cough notes that there is no standard approach for monitoring cough, and that in acute cough, there is a large placebo effect and considerable patient variability in response. Thus, “any parallel group study must be of a large size in order to convincingly show efficacy. Indeed, the only robust study demonstrating antitussive efficacy in acute cough is a meta-analysis of > 300 subjects.” (see above, Pavesi 2001) It is noteworthy that none of the individual studies cited above enrolled groups this large.

The American College of Chest Physicians (ACCP), in its Diagnosis and Management of Cough: Evidence-based Clinical Practice Guidelines, states, “Patients with acute cough (as well as PND [post-nasal drainage] and throat clearing) associated with the common cold can be treated with a first-generation A/D combination (brompheniramine and sustained-release pseudoephedrine)” [Irwin 2006].

CHPA concludes that these clinical trials in adults support the symptomatic benefits of cough and cold medications.

3.3.2 Pediatric Efficacy Data

Few pediatric trials met the enrollment criteria for adequately powered randomized controlled trials. The number of placebo-controlled RCTs is rather small. Inconsistent results observed for published pediatric studies in this area may be attributed in large part to the lack of sensitive and specific methodology with which to evaluate primarily subjective symptomatology. This is particularly compounded in the pediatric population, where children may have limited expressive capabilities and ability to respond regarding subjective symptoms in a consistent fashion, as well as variable levels of cooperation. Another limitation of certain studies is that some of the endpoints selected for study (e.g., appetite, crankiness, vomiting) were not appropriate for the mechanism of action of the test medications.

An important factor potentially contributing to the inconsistent results found in pediatric clinical trials in the literature is that most studies were underpowered. To test this hypothesis, a *post hoc* statistical analysis of 8 pediatric clinical trials was performed (see Appendix 2). It was found that, indeed, 7 of the 8 studies were vastly underpowered to show statistically significant differences based on the actual treatment effect observed. Each study would have required several hundred subjects per treatment arm, as opposed to the several dozen actually enrolled, in order to achieve statistical significance based on the observed magnitude of treatment effect.

3.3.2.1 Antihistamines

Sakchainanont conducted a study of antihistamines in children 1.5 months to 60 months of age with rhinorrhea with or without non-productive cough of 3 days duration. Subjective evaluations of nasal discharge, nasal turbinate edema, and cough were done, comparing CHLOR 0.35 mg/kg/day given 3 times daily (n=48) dose or clemastine fumarate 0.05 mg/kg/day in divided dose twice daily (n=48) or placebo 2 to 3 times daily (n=47) for 3 days. Study drugs were prepared in equal volumes to facilitate blinding. There was statistically significant improvement of every symptom in every group; only the character of nasal discharge was different,

with clemastine statistically significant vs placebo, while CHLOR was nearly statistically significant vs placebo. There was no difference between the 2 active groups. Slight drowsiness and sleepiness were the side effects evaluated, and these were not different from the placebo group [Sakchainanont 1990].

Paul enrolled 100 children aged 2 to 16.5 years (median 4.5 years) with nocturnal cough associated with URI. Patients were stratified by ages 2 to 5 years, 6 to 11 years, and 12 to 18 years of age, and given diphenhydramine (DPH) 1.25 mg/kg of body weight (n= 33) or placebo (n=34) as a single dose 30 minutes before bedtime. The remaining 33 children were randomized to receive DXM (see Antitussives section below). Parents made subjective assessments of frequency, severity and bothersome nature of nocturnal cough, and of sleep quality for children and parents. There were no significant differences between treatment groups, although a trend for better sleep quality was noted for the DPH group [Paul 2004].

Yoder studied a subset of the Paul subjects. Children 6 to 18 years of age (median age 7.5 years) with nocturnal cough related to URI, who were treated for 2 days with DPH 1.25 mg/kg/dose (n=12) or placebo (n=13) at bedtime, were evaluated using the children's self-assessment of cough relief and sleep quality. There were no significant differences between treatment groups, but a trend for better sleep quality in the DPH group was noted [Yoder 2006].

3.3.2.2 Decongestants

Martinez-Gallardo enrolled 65 children with common colds, age 2 to16 years in a RCT of PSE alone (n=15) or in combination with naproxen (NAP) (n=20), placebo for PSE (n=14) or placebo for the combination (n=16) for 5 days. The dose of each component escalated with each age group (2 to 5 years PSE 15 mg with or without NAP 50 mg; 6 to 9 years PSE 30 mg with or without NAP 100 mg; 10 to 12 years PSE 45 mg with or without NAP 150 mg; and 13 to 16 years PSE 60 mg with or without NAP 200 mg). The physician evaluated cold signs and symptoms after 3 and 5 days, and reported significantly shorter duration of nasal obstruction, mucosal edema, lacrimation, and headache with the combination. Greater symptom relief was reported on the 3rd and 5th days with the combination compared with the other groups, between which there were no differences [Martinez-Gallardo 1994].

3.3.2.3 Antitussives

In the above study by Paul, 33 subjects were randomized to receive DXM rather than DPH. Children age 2 to 5 years received DXM 7.5 mg, 6 to 11 year olds received 15 mg, and 30 mg was given to those more than 11 years of age. Subjective assessments of cough by parents showed improvement for all outcomes for all groups, with no statistical difference between groups in providing nocturnal symptom relief.

In the Yoder study described above (subset of the Paul study), children age 6.2 years to 16.5 years (median age 7.5 years) were randomized to receive DXM (n=12) or placebo (n=13) in the same fashion as in the Paul study. There were no significant differences from placebo regarding symptom relief [Yoder 2006].

3.3.2.4 Expectorants

No published single-ingredient RCTs of patients with the common cold were identified.

3.3.2.5 Combination products

Taylor conducted a RCT of nocturnal cough of less than 14 days' duration in 2 cohorts: children aged 18 months to 5 years (mean age 4.7 years) received either GUA 50 mg with DXM 7.5 mg, or GUA 50 mg with codeine 5 mg, or placebo; children aged 6 to 12 years received GUA 100 mg with DXM 15 mg, or GUA 100 mg with codeine 10 mg, or placebo (total n for GUA with DXM = 19; total n for GUA with codeine = 17; placebo n = 13). Parents provided subjective morning assessments of cough and sleep. Neither combination was superior to placebo in treating nocturnal cough at the doses given in either age group [Taylor 1993].

Hutton enrolled children age 0.5 to 5 years (mean age 25 months) with signs of URI. This RCT evaluated a combination of BROM 4 mg/5 ml with PE 5mg/ml and phenylpropanolamine (PPA) 5 mg/5 ml (n=36) or placebo (n=27) given 3 times daily so that the BROM dosage was 0.5 to 0.75 mg/kg/day for 2 days. Parents' subjective assessments of symptoms (congested or runny nose, breathing trouble, fever, cough, decreased appetite, crankiness, sleep disturbance, and excessive sleepiness) were performed at 48 hours. There were no differences from placebo in individual or composite symptom score changes [Hutton 1991].

Clemens enrolled children aged 0.5 to 5 years with acute (<7 days) URI, who received placebo (n=31) or BROM 2 mg/5 ml with PPA 12.5 mg/ml (n=28): 0.5 teaspoon for age 6 months to 2 years, and 1 teaspoon for ages 2 to 5 years, no more often than every 4 hours and no more than 4 doses, for 48 hours. Parents made subjective assessments 2 hours after each dose, of changes in symptoms (runny nose, nasal congestion, and cough) and whether the child was sleeping. No statistically significant differences in symptom improvement were observed between groups, but a higher proportion of treated children were sleeping 2 hours after a dosage of active medication (46.6% vs 26.5%) and this difference was statistically significant [Clemens 1997].

Reece evaluated cough in children age 2 months to 12 years when treated with placebo or 1 of 2 combination products: A (each 5 ml contained PPA 12.5 mg with pheniramine 6.25 mg and DXM 15 mg and ammonium chloride 90mg) or B (each 5 ml contained DXM 7.5mg with PPA 8.75 mg and glyceryl guaiacolate 37.5 mg and alcohol 5%). Each of these was dosed according to an age chart that provided dosing for <2 years, 2 to 6 years, and 7 to 12 years. There was an inpatient cohort (n=22; ages 2 months to 9 years; average age 1.9 years) that employed a tape recording for cough counts, and an outpatient cohort (n=43; age 2 months to 12 years; average age 3.6 years) that relied on parental assessment of cough. The authors stated that in the inpatient study the superiority of the antitussive medications was so obvious that statistical analysis was not necessary (the data in the paper have now been analyzed by a statistician and found not to be statistically significant). The outpatient study did not demonstrate significant differences in treatments [Reece 1966].

Korppi enrolled 50 children age 1 year to 10 years (mean age 3.8 years) with cough associated with URI in a RCT comparing DXM 1.5mg/ml (n=24) with or without salbutamol 0.2 mg/ml vs placebo (n=26). Subjects age < 7 years received 5 ml, subjects ≥ 7 years received 10 ml, 3 times daily for 3 days. Parents' subjective assessments of symptoms and daily assessment of general condition revealed that symptom scores dropped significantly in all groups, but there was no difference between groups, neither for symptom scores nor in reported general condition on any of the 3 days [Korppi 1991].

In addition to the reviews of cough and cold preparations described previously which included comments regarding pediatric use, the American Academy of Pediatrics (AAP) Committee on Drugs has commented on the use of dextromethorphan-containing cough remedies in children. This statement regarding the treatment of cough is apparently the only cough and cold medication on which AAP offers an opinion. AAP concluded that no well-controlled studies support the efficacy and safety of these products for the treatment of cough in children, and note that dosing is derived from extrapolation of adult data. The Committee on Drugs calls for further research of these preparations in children.

3.4 Summary Points

- Evidence for the efficacy and safety of OTC cough and cold medicines based on randomized, placebo-controlled trials in adults are prevalent in the literature.
- The results of pediatric studies of OTC cough and cold medicines have been inconclusive to date.
    - There are considerable challenges and limitations to the study of cough and cold medicines in pediatrics related to study design and lack of sensitive, relevant endpoints.
    - The majority of pediatric randomized, controlled trials have been underpowered.
    - Recommendations by professional, authoritative bodies to not use certain ingredients in young children relate, for the most part, to the lack of robust clinical trial data in this patient population.
- CHPA concludes that it would be beneficial to expand the body of evidence for the use of cough and cold medicines in children.
    - Studies must be appropriately powered to achieve statistical significance.
    - Appropriate efficacy endpoints based on the mechanism of action of the test medications must be employed.
    - The field will be advanced by the development of robust, validated methodology for evaluating the signs and symptoms of the common cold.

4 EXTRAPOLATION OF PHARMACOKINETIC DATA TO DETERMINE APPROPRIATE DOSING IN CHILDREN

4.1 Key Points

- Traditionally, pediatric doses, including those for OTC monograph drugs, were based on age-weight rules. Extrapolation with pharmacokinetic data is currently used to select pediatric doses, along with safety information in children. Where available, pharmacodynamic and/or efficacy data are also used to select doses.
- Pediatric and adult pharmacokinetics (clearance, half-life, and/or distribution volume) do not need to be the same to extrapolate pediatric doses that would correspond with adult efficacy. Instead, data are used to select doses that provide comparable blood levels as adults, expressed as total and maximum drug exposure (AUC_{INF} and C_{MAX}).
- Available pediatric pharmacokinetic data for pseudoephedrine and chlorpheniramine confirm the appropriateness of recommended OTC monograph doses for children 2 to <12 years, and 6 to < 12 years, respectively.
- Member companies of CHPA are committed to obtain additional pharmacokinetic data for other OTC cough and cold drugs, where needed, to better characterize and confirm dosing in children.

This section provides an overview of pediatric dosing from early years when doses were based on general age-weight rules without an understanding of drug disposition in children. Such rules formed the basis of recommended pediatric doses of OTC cough and cold drugs in the 1976 monograph review. Because of the evolution of pediatric clinical research through the 1990s, pharmacokinetic studies in children are more common, and the data are used to determine appropriate doses. A sufficient amount of pharmacokinetic data is available in children and adults for two OTC cold drugs with which to show a relationship between dose and drug exposure. The findings across studies and age groups are included in this section, whereas listings of the data are located in Appendix 3.

4.2 Dosing by Pediatric Age Group

Historically, adult doses provide the reference point for therapy in children with adjustment for body size. The age and body weight or surface area of children were used to adjust adult doses. For example, Clark's weight rule was often used to approximate dose by dividing the child's weight in pounds by 150 (or weight in kilograms by 70), and multiplying

the result by the adult dose [Munzenberger 1980]. By contrast, the majority of chemotherapy regimens and trials specify doses of cytotoxic drugs normalized to body surface area in m^2 [Sharkey 2001]. However, estimation of body surface area in pediatric patients is particularly problematic, as conventional nomograms require accurate determination of both height and weight.

Doses of pharmacologically active agents in children are generally provided by age group. The 1994 Pediatric FDA Final Rule [59 FR 64240], as well as current guidelines [ICH E11 2000] on clinical investigations of drugs in pediatric populations consider the following groups:

- Term newborn infants (0 to 27 days)
- Infants and toddlers (1 month to < 2 years)
- Children (2 to < 12 years)
- Adolescents (12 to 16 or 18 years)

These age groups generally reflect developmental stages – changes after birth; early growth spurt; gradual growth from 2 to <12 years; and pubertal and adolescent growth spurt and development towards adult maturity. Although not necessarily related to clinical differences, the age group 2 to < 12 years, is sometimes further subdivided in terms of the child's ability to accept and use different pharmaceutical dosage forms: pre-school children (2 to < 6 years) and school children (6 to < 12 years).

4.3 Basis for Pediatric Dosing in the OTC Cough and Cold Monograph

The 1976 FDA Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products discussed the best approach to pediatric dosage [41 FR 38312]. The panel concluded, "the dosage that will produce optimum therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age, weight, and metabolic, pathological, or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered general guides" [41 FR 38333].

The panel also commented that dosing based on the "age of the child, although convenient, may be the least reliable method because of the large variation in the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the panel concluded that dosage recommendations based on age are the most reasonable since they would be most easily understood by the consumer" [41 FR 38333].

After consultation with a group of experts in pediatric drug therapy, the Panel recommended the following pediatric doses based on weight and age: “For infants under 2 years of age, the pediatric dosage should be established by a physician. For children 2 to under 6 years of age, the pediatric dosage is ¼ the adults dosage; for children 6 to under 12 years of age, the dosage is ½ the adult dosage” [FR 41176 p 38333]. This dosing pattern generally follows Clark’s weight rule, which is illustrated in Table 4.1 for three cough and cold drugs.

Table 4.1 Pediatric Single Doses for OTC Drugs in the Cold/Cough Monograph

	12 to adults	**6 to < 12 y**	**2 to < 6 y**	**Under 2 y**
Weight Range (lb)	-----	48 to 95	24 to 47	< 24
Mean Weight (lb)	150	71.5	35.5	12
Clark’s Weight Rule	150/150 = 1	71.5/150 = 0.48	35.5/150 = 0.24	12/150 = 0.08
Monograph Dose	1	½	¼	Consult a doctor
Examples				
Pseudoephedrine	60 mg	30 mg	15 mg	Consult a doctor
Chlorpheniramine	4 mg	2 mg	Consult a doctor	Consult a doctor
Dextromethorphan	30 mg	15 mg	7.5 mg	Consult a doctor

4.4 Drug-Exposure Basis of Pediatric Dosing: The Current Method

More recently, pharmacokinetic studies in children, including infants and toddlers, have increased our understanding of drug disposition in this population. These data are used to select pediatric doses that provide blood levels similar to those observed in adults [ICH E11 2000]. Pediatric safety data are also considered in the selection of pediatric doses, and where possible, either pharmacodynamic and/or efficacy data are considered as well.

Extrapolation from adult efficacy to children may be appropriate for some therapeutic classes of drug, and examples include prescription antihistamines for allergic rhinitis and proton pump inhibitors for gastrointestinal reflux disease[1]. The basis for extrapolation (per the approved product labeling[2]) is “the likelihood that the disease course, pathophysiology, and the drug’s effect are substantially similar to that of adults”. Recommended doses of these products for pediatric populations are then based on cross-study comparisons of pharmacokinetic data in adults and children and on the drug’s safety data profile in the

[1] www.fda.gov/cder/pediatric/labelchange.htm, Prea_label_post-mar_2_mtg.htm, Summaryreview.htm, Accessed September 5, 2007

[2] Allegra®, Claritin®, Clarinex®, Zytec®, and Xytal®

various age groups. Although drug clearances may differ, recommended doses are usually those that provide comparable total (AUC_{INF}) and maximum drug exposure (C_{MAX}) among different age groups.

4.5 Recommended Doses for Pediatric OTC Products Requiring Preapproval by FDA

Two or more monograph ingredients may be combined into a cough and cold product formulation and be marketed without preapproval by FDA. However, preapproval is required if one of the OTC drugs is regulated under a New Drug Application (NDA). Three pediatric cold (NDA 21-128; 21-373) and allergy-sinus (NDA 21-587) combination OTC products required additional clinical studies for approval. Pseudoephedrine, with and without chlorpheniramine, in combination with ibuprofen, had to follow *de facto* the NDA process, as ibuprofen is an NDA drug.

The pediatric information requested by FDA was pediatric pharmacokinetic data on the active ingredients in the target population to assess potential drug interactions and doses. In addition, open-label safety studies in children were requested for the combination of cold and allergy drugs with ibuprofen because there was no history of combined use in the pediatric population. The objective of these safety studies was to characterize the adverse event profile of the proposed OTC combination products. Table 4.2 summarizes the pediatric clinical programs for each drug application.

The selection of pediatric doses for children from 2 to < 12 years was not straightforward because ibuprofen and pseudoephedrine have a different number of weight-age divisions for dosing. OTC analgesics have more divisions than OTC cough and cold medications, which decrease the differences between the minimum and maximum doses within each pediatric age group (2 to < 6 years and 6 to < 12 years). The sponsor of NDA 21-128 dosed the children by mg/kg in the pharmacokinetic and open-label safety studies, and proposed the dosing schedule associated with ibuprofen summarized in Table 4.3. The dosing schedule associated with pediatric OTC cough and cold medications with fewer weight-age divisions was approved for the combination product based on the upper limit of doses permitted by the monograph in each age group. There were no pharmacokinetic interactions between active ingredients tested, and the overall safety profile was consistent with each individual ingredient's established adverse event profile. The approved dosing schedule is summarized in Table 4.4.

Table 4.2 Pediatric Information Submitted in Three NDAs for OTC Combination Cold/Allergy/Sinus Products

NDA	Drug Product	Indication and Pediatric Clinical Program
21-128	IBU 100 mg; PSE 15 mg per 5 mL suspension ***Dosing Chart*:** Under 2 years — Ask a Doctor 2 to 5 years — 1 tsp 6 to 11 years — 2 tsp	***Indication:*** Temporarily relieves these cold, sinus, and flu symptoms: • nasal and sinus congestion • stuffy nose • minor body aches and pains • headache • fever • sore throat ***Pediatric Clinical Program*** • Multiple-dose pediatric pharmacokinetic study in healthy children, ages 4 to 11 years (n=24) • Safety study in children with symptomatic rhinitis, ages 2 to 11 years (n=114)
21-373	IBU 100 mg; PSE 15 mg per 5 mL suspension ***Dosing Chart*:** Under 2 years — Ask a Doctor 2 to 5 years — 1 tsp 6 to 11 years — 2 tsp	***Indication:*** Temporarily relieves these cold, sinus, and flu symptoms: • nasal and sinus congestion • stuffy nose • minor body aches and pains • headache • fever • sore throat ***Pediatric Clinical Program*** • Single-dose pediatric pharmacokinetic study in children ages 2 to 5 years (n=23) • Single-dose pediatric pharmacokinetic study in healthy children, ages 6 to 11 years (n=31) • Safety study in children with symptomatic rhinitis or sinusitis, ages 2 to 11 years (n=106)
21-587	IBU 100 mg; PSE 15 mg; CPM 1 mg per 5 mL suspension ***Dosing Chart*:** Under 6 years — Ask a Doctor 6 to 11 years — 2 tsp	***Indication:*** For the temporary relief of symptoms associated with hay fever or other upper respiratory allergies, and the common cold: • runny nose • itching of the nose and throat • sneezing • sinus pressure • minor body aches and pains • nasal congestion • headache • fever ***Pediatric Clinical Program*** • Single-dose pediatric pharmacokinetic study in children with allergic rhinitis, ages 6 to 11 years (n=30) • Safety study in children with upper respiratory allergies, ages 6 to 11 years (n=111)

Key: CPM – chlorpheniramine maleate, IBU – ibuprofen, PSE – pseudoephedrine HCl

Table 4.3 Dosing Schedule Proposed for the Ibuprofen-Pseudoephedrine Suspension, 100-5 mg/5 mL (NDA 21-128)

Weight Range (lb)	Age (years)	Dose[a] (teaspoon)	Ibuprofen Dose (mg)	Pseudoephedrine HCl Dose (mg)
Under 24	Under 2	Consult Doctor	Consult Doctor	Consult Doctor
24 - 35	2 - 3	1	100	15
36 - 47	4 - 5	1 ½	150	22.5
48 - 59	6 - 8	2	200	30
60 - 71	9 - 10	2 ½	250	37.5
72 - 95	11	3	300	45

a: Dosage may be repeated every six to eight hours, but not more than four times a day.

Table 4.4 Approved Dosing Schedule for NDAs 21-128 and 21-373

Weight Range (lb)	Age (years)	Dose[a] (teaspoon)	Ibuprofen Dose (mg)	Pseudoephedrine HCl Dose (mg)
Under 24	Under 2	Consult Doctor	Consult Doctor	Consult Doctor
24 - 47	2 - 5	1	100	15
48 - 95	6 - 11	2	200	30

a: Dosage may be repeated every six hours, but not more than four times a day.

Subsequently, the dosing schedules for the two other pediatric OTC combination products (NDA 21-373 and 21-587) were based on these dosing schedules for the cold and allergy drugs with fewer weight-age breaks than analgesics, and on the upper limit of doses in the monograph. For the triple combination suspension (ibuprofen-pseudoephedrine-chlorpheniramine), efficacy in children ages 6 to < 12 years at the approved doses was extrapolated from adult efficacy demonstrated with the adult combination product (NDA 21-441). In addition, there were no pharmacokinetic interactions among the three drugs in children, and the safety profile was consistent with each individual drug's adverse event profile.

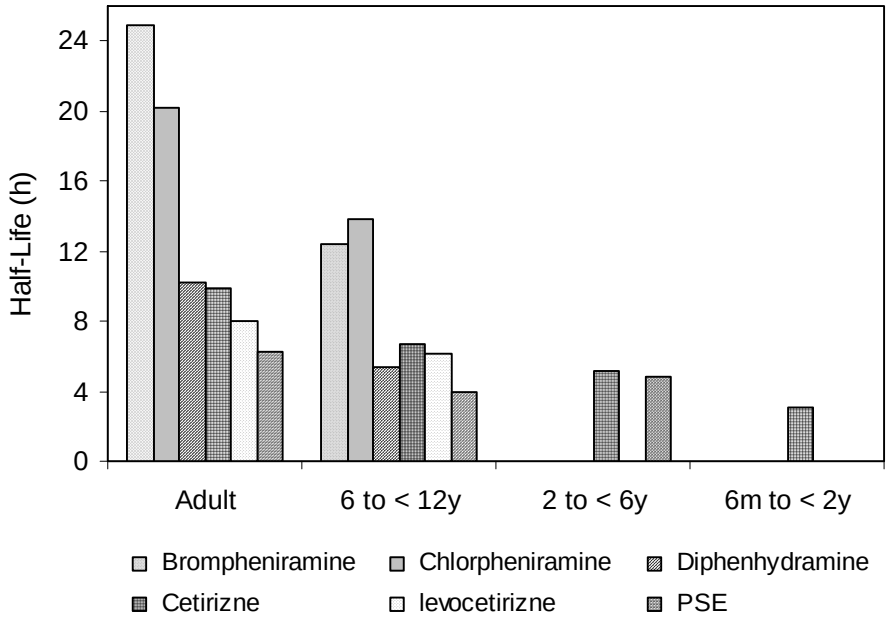
4.6 Insights From Available Pediatric Pharmacokinetic Data for OTC Drugs

Pediatric pharmacokinetic data are available for orally administered pseudoephedrine [McNeil 1999, Auritt 1981, Simons 1996, Wyeth 2002a, Wyeth 2004], chlorpheniramine [Wyeth 2004, Simons 1982], brompheniramine [Simons 1999], and diphenhydramine

[Simons 1990] in children ages 6 to < 12 years. Data for pseudoephedrine are also available in children ages 2 to < 6 years [McNeil 1999, Wyeth 2002a]. Compared with adults, weight-adjusted oral clearances are higher and half-lives are shorter in children, which is generally true for many drugs, although there are exceptions.

A comparison of mean values of half-life is shown in Figure 4.1. Estimates of half-life are used to determine dose intervals, time to steady state, and drug accumulation in the blood with multiple dosing. Because dosing intervals for OTC drugs are generally the same for adults and children, the shorter half-lives indicate that steady state would be reached in shorter times and that there would be less drug accumulation in children.

Figure 4.1 Cross-Study Comparison of Mean Half-Lives for OTC Drugs and Two Prescription Antihistamines



Urine metabolite data in older children have been published for pseudoephedrine [Simons 1996] and chlorpheniramine [Simons 1983]. Elimination of pseudoephedrine is primarily through the renal route, with about 75% of an administered dose excreted unchanged in urine by adults [Nieder 1988]. In one pharmacokinetic study in children, urine was collected from two subjects receiving 30 mg pseudoephedrine. The recovery of unchanged drug over 24 hours is comparable with adults at 66% of the dose [Simons 1996].

Chlorpheniramine is rapidly metabolized by the liver to mono and di-demethylated metabolites, and to polar oxidative metabolites. A role of cytochrome P450 2D6 has been

shown in the metabolism of chlorpheniramine. After a single-dose of chlorpheniramine in 11 children, the recovery of drug and metabolites over 48 hours was 11.3 ± 6.7% chlorpheniramine, 23.3 ± 11.1% demethylchlorpheniramine, and 9.6 ± 9.4% di-demethyl-chlorpheniramine [Simons 1983]. The relative percents of each species excreted are consistent with those in adults. However, the absolute percents are about double those in adults, which most likely reflect the incomplete 24-hour collection of urine in adults [Kabasakalian 1968].

Urine metabolite data in neonates and infants up to 12 months of age have recently been published for dextromethorphan [Blake 2007]. The data indicate that cytochrome P450 2D6 activity is detectable and concordant with genotype by two weeks of age, shows no relationship with gestational age, and does not change with post natal age up to 12 months. In contrast, dextromethorphan N-demethylation developed more slowly over the first year of life. However, the pharmacokinetic and clinical relevance of this finding is unknown and would need further investigation.

4.7 Confirmation of Current OTC Pseudoephedrine Doses in Children, Ages 2 to < 12 Years

Pediatric and adult pharmacokinetics (clearance, half-life, and/or distribution volume) do not need to be the same to extrapolate pediatric doses that would correspond to adult efficacy. Instead, data are used to select doses that provide comparable blood levels as adults, expressed as total and maximum drug exposure (AUC_{INF} and C_{MAX}, respectively). In this section, pediatric pharmacokinetic data are used to confirm the appropriateness of recommended OTC pseudoephedrine doses in children that were originally based on Clark's weight rule.

4.7.1 Indication and Mechanism of Action

Oral pseudoephedrine is indicated for the temporary relief of nasal congestion, a prominent symptom of the common cold. It causes vasoconstriction by activating the postsynaptic α-adrenergic receptors indirectly through the displacement of norepinephrine [Hoffman 2001]. Targeted adrenergic receptors are located on the muscles lining the walls of blood vessels in the nasal passages. When activated by pseudoephedrine, the muscles contract, causing blood vessels to constrict. These constricted blood vessels allow less fluid to enter the nose, throat, and sinus linings, which result in decreased inflammation of nasal membranes as well as decreased mucous production [Empey 1981]. Thus, by constriction of blood

vessels, mainly those located in the nasal passages, pseudoephedrine causes a decrease in the symptoms of nasal congestion.

4.7.2 Available Pseudoephedrine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for pseudoephedrine in 119 children ages 2 through 11 years old were collected from a multiple-dose study [McNeil 1999], two published single-dose studies [Auritt 1981, Simons 1996], and three single-dose studies for pediatric cold and allergy-sinus OTC products [Wyeth 2002a, Wyeth 2004]. FDA summarized data for the latter studies as part of the basis of approval for new drug applications, NDA 21-373 and 21-587, and these summaries are publicly available per the Freedom of Information Act. The dose-independent pharmacokinetic parameters, oral clearance (CL/F), half-life ($t_{½}$), and apparent distribution volume (Vd/F) from studies in children and adults are listed in Table 4.5, which is located in Appendix 3. A listing of administered doses and drug exposure parameters (AUC_{INF} and C_{MAX}) is also located in Appendix 3 as Table 4.6.

For a cross-study comparison, three graphs of maximum pseudoephedrine exposure by dose for children ages 2 to < 6 years and 6 to < 12 years, and for adults are shown in Figure 4.2. The relationship between mean C_{MAX} values and dose is linear in each group, although the slopes are different. A horizontal dashed line is drawn across the figure at the point where a vertical line is drawn up from the 60-mg adult dose. This horizontal line intersects the slope for each children's group, which shows that the recommended pediatric OTC doses of 15 and 30 mg pseudoephedrine provide maximum concentrations comparable to that for a 60-mg dose in adults.

Mean values for total systemic exposure (AUC_{INF}) among age groups and studies are plotted by dose in Figure 4.3. Again, the relationship between mean AUC_{INF} values and dose is linear in each group, although the slopes are different. This graphical representation shows that the overall mean AUC_{INF} of the 30-mg dose in older children is comparable to adults (only about 14% lower). For the younger children, ages 2 to < 6 years, the overall mean AUC_{INF} is about 34% lower than that in adults. These differences reflect the higher, weight-adjusted clearances of pseudoephedrine in children. Yet, importantly, the average values for younger and older children fall between the total systemic exposures for the 30- and 60-mg doses in adults, which are both effective doses.

Figure 4.2 Means of Maximum Systemic Exposure by Single Pseudoephedrine Dose in Children and Adults

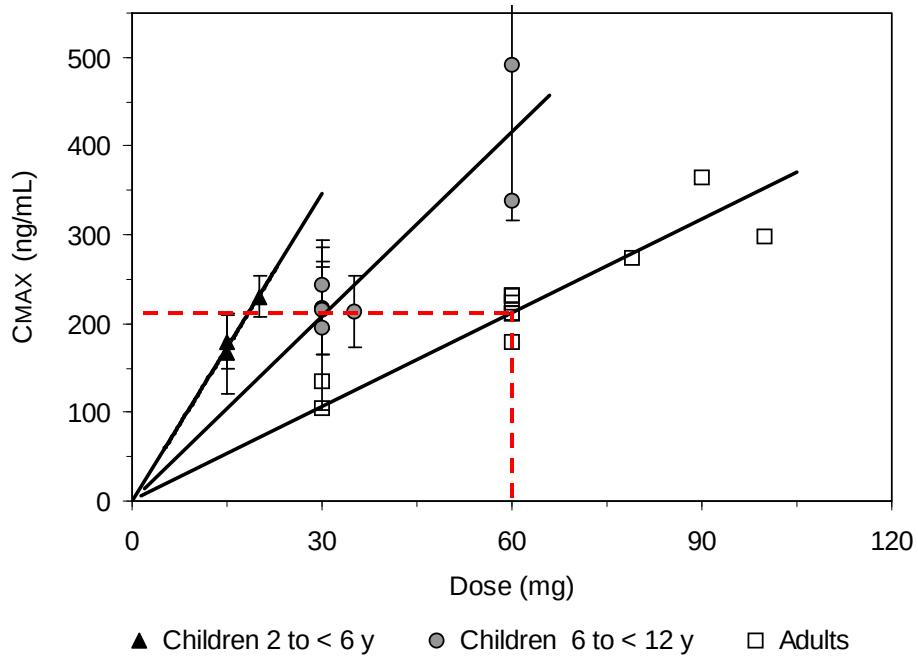
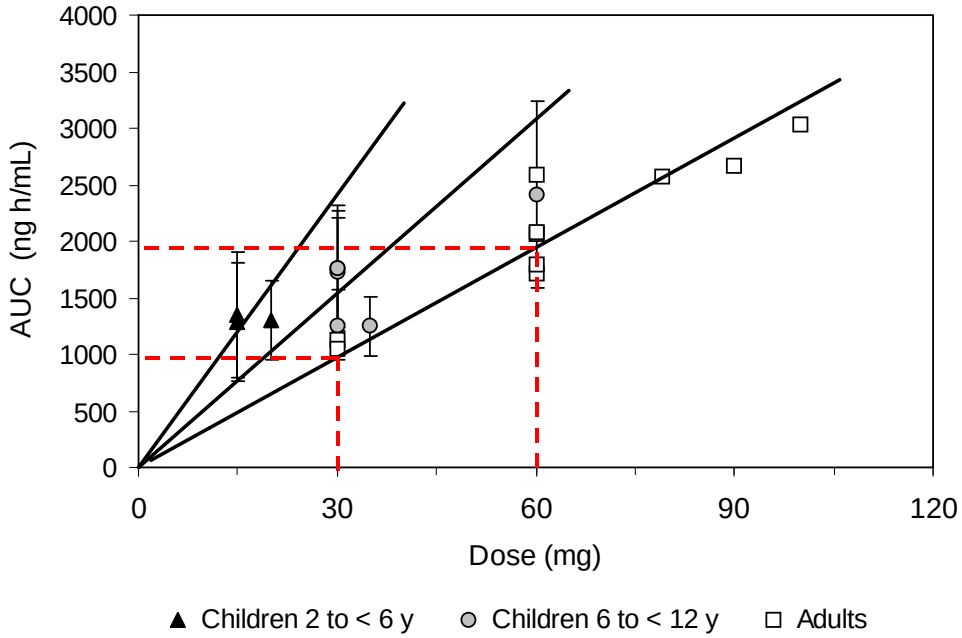


Figure 4.3 Means of Total Systemic Exposure by Single Pseudoephedrine Dose in Children and Adults



Pseudoephedrine 60 mg was found to be a generally recognized safe and effective medication for OTC use as an oral nasal decongestant by FDA's Review Panel based on a series of clinical studies [FR 41176]. One placebo-controlled study, which included an objective measure, showed the 30-mg dose having a significant decrease in resistance to flow in nasal congestion. A 30-mg dose of pseudoephedrine, when combined with ibuprofen 200 mg and/or chlorpheniramine 2 mg, has been shown to be effective in at least two out of three double-blind, placebo-controlled clinical trials [McNeil 1991, Meltzer 2004]. Results of these studies on assessment of relief of nasal symptoms are summarized in Table 4.5.

Table 4.5 Additional Supporting Efficacy for a 30-mg Pseudoephedrine Dose in Adults

Study (Clinical Model)	Design	Treatments	Nasal Symptom Endpoints	Results
McNeil 1991 Study 86-683 (sinus headache)	DB, PC, DR, PL, SD, MC (n=348)	I400/P60 I200/P30 Pbo	For all four summary measures of sinus congestion: SCID, MAXCID, TOTCOR, MAXCOR	I400/P60 = I200/P30 > Pbo
Meltzer 2004 (seasonal allergic rhinitis)	DB, PC, DR, PL, MD, MC (n=1044)	I400/P60/C4 I200/P30/C2 P30/C2 Pbo	OATSS and OATASS	I400/P60/C4 = I200/P30/C2 I400/P60/C4 > Pbo I200/P30/C2 > Pbo P30/C2 > Pbo I200/P30/C2 > P30/C2

Key: C - chlorpheniramine, DB – double blind, DR – dose response, I – ibuprofen, P - pseudoephedrine, Pbo – placebo, PC – placebo control, PL – parallel group, MC – multiple centers, MD – multiple dose, SD – single dose.

Nasal Symptom Endpoints:

Sinus congestion: SCID – sinus congestion intensity difference, MAXCID – maximum congestion intensity difference, TOTCOR – total congestion relief, and MAXCOR – maximum congestion relief.

OATSS – Overall average total symptom score: nasal congestion, sneezing, rhinorrhea, itchy nose/throat/palate, itchy/watery/red eyes, and pain.

OATASS - Overall average total antihistamine symptom score: sneezing, rhinorrhea, itchy nose/throat/palate, itchy/watery/red eyes

4.8 Confirmation of Current OTC Chlorpheniramine Doses in Children, Ages 6 to < 12 Years

Pediatric and adult pharmacokinetics (clearance, half-life, and/or distribution volume) do not need to be the same to extrapolate pediatric doses that would correspond to adult efficacy. Instead, data are used to select doses that provide comparable blood levels as adults, expressed as total and maximum drug exposure (AUC_{INF} and C_{MAX}, respectively). In this section, pediatric pharmacokinetic data are used to confirm the appropriateness of the recommended OTC chlorpheniramine dose in children that was originally based on Clark's weight rule.

4.8.1 Indication and Mechanism of Action

Chlorpheniramine is indicated to alleviate rhinorrhea and sneezing due to the common cold. The mechanism by which first-generation antihistamines reduce nasal discharge due to the common cold is believed to occur through anticholinergic effects. The main control of nasal secretion is autonomic (cholinergic), with parasympathetic stimulation increasing secretion [Lund 1996].

4.8.2 Available Chlorpheniramine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for chlorpheniramine in 41 children ages 6 through 11 years old were collected from a published study [Simons 1982] and a study submitted to FDA to support approval of a pediatric triple ingredient OTC product [Wyeth 2004]. FDA had summarized data for the latter study as part of the basis of approval, and this summary is publicly available. The dose-independent pharmacokinetic parameters, oral clearance (CL/F), half-life ($t_{½}$), and apparent distribution volume (Vd/F) from studies in children and adults are listed in Table 4.7, which is located in Appendix 3. A listing of administered doses and drug exposure parameters (AUC_{INF} and C_{MAX}) is also located in Appendix 3 as Table 4.8.

For a cross-study comparison, two graphs of maximum chlorpheniramine exposure by dose for children ages 6 to < 12 years and for adults are shown in Figure 4.4. The relationship between mean C_{MAX} values and dose is linear in each group, although the slopes are different. A horizontal, dashed line is drawn across the figure at the point where a vertical line is drawn up from the 4-mg adult dose. This horizontal line intersects the slope for the children's group, which shows that the current pediatric OTC dose of 2 mg chlorpheniramine provides maximum concentrations comparable to that for a 4-mg dose in adults.

Mean values for total systemic exposure (AUC_{INF}) among age groups and studies are plotted by dose in Figure 4.5. Mean AUC_{INF} for the 2-mg chlorpheniramine dose in children, ages 6 to < 12 years, is about 21% lower than the overall mean across studies for the 4-mg dose in adults. This difference reflects the higher, weight-adjusted clearance of chlorpheniramine in children. Yet, the mean value for children falls within the range of total systemic exposures for 2- and 4-mg doses in adults. Although the 2-mg chlorpheniramine dose has not been commonly studied in adults, evidence of efficacy versus placebo has been recently published for this dose when combined with 30 mg of pseudoephedrine [Meltzer 2004].

Figure 4.4 Means of Maximum Systemic Exposure by Single Chlorpheniramine Dose in Children and Adults

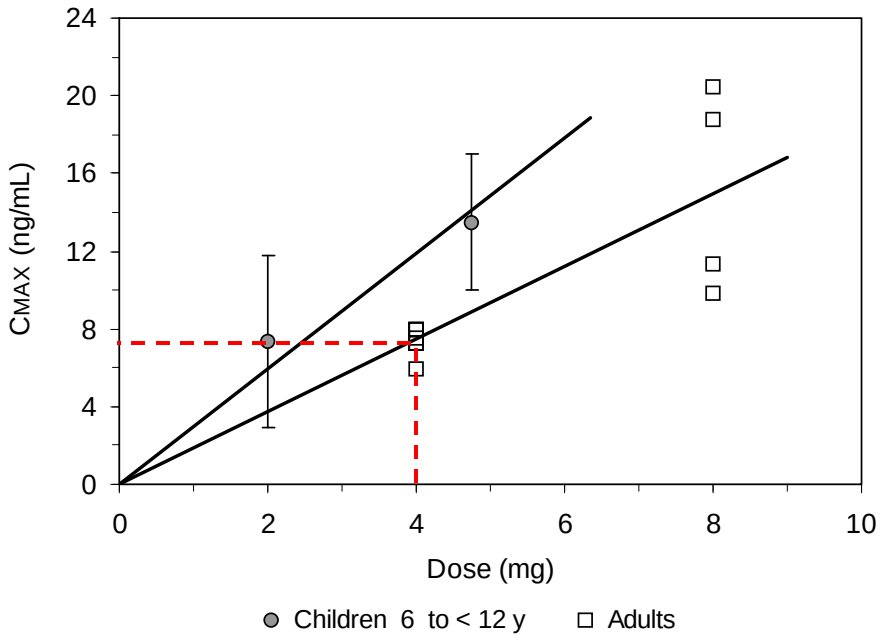
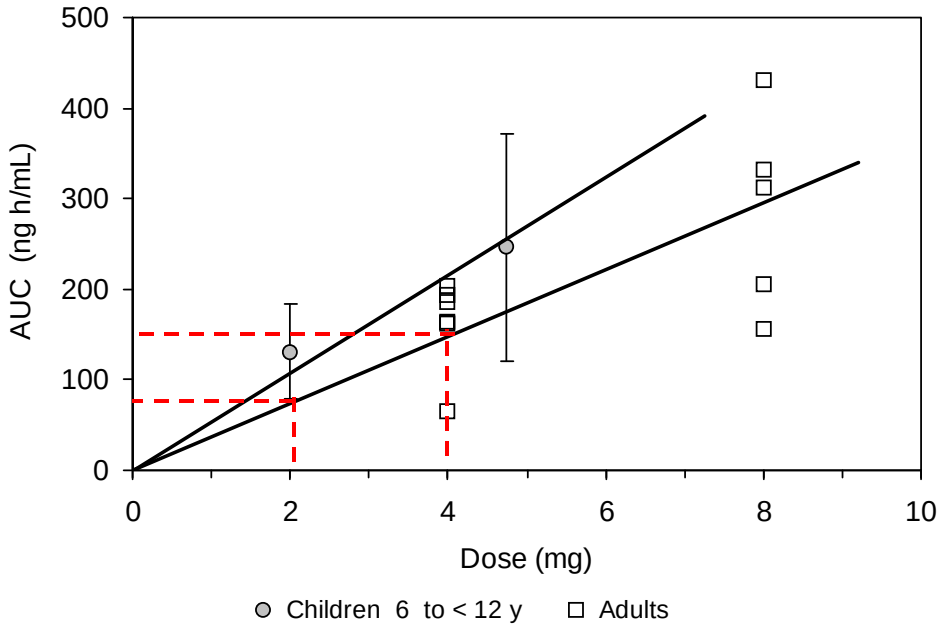


Figure 4.5 Means of Total Systemic Exposure by Single Chlorpheniramine Dose in Children and Adults



4.9 Summary

Cross-study comparisons of pediatric and adult, single-dose pharmacokinetic data indicate that recommended OTC pediatric doses for pseudoephedrine and chlorpheniramine provide comparable maximum drug exposures to those in adults. Total systemic exposures were within ranges of those from effective adult single doses. In practice, multiple doses of OTC cough and cold medications are administered such that average blood concentrations of ingredients would be somewhat higher, depending on the drug's half-life and dosing interval. Likewise, maximum exposure after multiple doses would be higher, although there is less accumulation in children due to the drugs' shorter half-lives.

Every drug has unique properties that may potentially affect its disposition differently in children and adults. As such, pediatric pharmacokinetic data are needed to assess doses for other OTC drugs by age group. CHPA member companies are committed to conducting pharmacokinetic studies in children 2 to < 12 years of age for the following ingredients: dextromethorphan, phenylephrine, guaifenesin, brompheniramine, diphenhydramine, and doxylamine. As shown in this section, extrapolation of pharmacokinetic data to determine doses is a practical approach.

5 SAFETY REVIEW OF PEDIATRIC OTC COUGH AND COLD MEDICINES

5.1 Key Points

- Safety data findings from prospective clinical trials support that recommended doses of over-the-counter (OTC) cough and cold medicines are well tolerated in children.
- Given the extensive use of pediatric OTC cough and cold products, reports with major effects and fatal outcomes are rare. The limited number of fatalities that have been reported are mostly in children under 2 years of age, resulting from caregivers administering supratherapeutic doses of these medicine or secondary to accidental overdoses following ingestion of these products by curious young children who gain accidental and unsupervised access.
- In children <6 years of age, inadequate poison prevention in the home (inadequate measures to keep medicines out of the reach of children) leads to a significant number of accidental exposures. Despite this, overdoses resulting in toxicity and requiring healthcare evaluation and treatment are rare.
- Collectively, data from various sources suggest that medication/therapeutic errors with OTC cough and cold products in children may lead to unintentional overdose when:
    - Products are administered without using an appropriate measuring device
    - Confusion occurs between different product forms and varying concentrations
    - Multiple products containing the same or similar active ingredients are administered at the same time
    - Adult products are administered to children
    - Product labels do not provide dosing information and there is miscommunication between caregivers and healthcare providers, especially in children under 2 years of age
    - OTC cough and cold products are given for unlabeled uses (e.g. sedation) that may contribute to overdose.

In its Citizen Petition of March and May, 2007 (Docket 2007P-0074), The Baltimore City Health Department (BHD) cites evidence from the American Association of Poison Control Centers (AAPCC) and from the Maryland Poison Center (MPC). CHPA and its member companies requested and received additional information from both the American Association of Poison Control Centers (AAPCC) and the Maryland Poison Center (MPC), which is provided.

The BHD Petition also notes reports of fatality from the published literature, as well as four unpublished reports from the Maryland Office of the Medical Examiner. In this regard, CHPA has commissioned the Rocky Mountain Poison and Drug Center (RMPDC) to convene an independent expert medical panel whose objective is to review all available fatality cases in children under the age of 12 years associated with the use of OTC cough and cold products. The expert panel has obtained fatality cases from manufacturers' post-marketing adverse event reports (MedWatch Forms), the American Association of Poison Control Centers (AAPCC), the published English medical literature (including literature cited in the Baltimore Petition) and the Maryland Office of the Medical Examiner. At the time of this submission, the expert panel's review is still in progress.

CHPA and its member companies are also continuing the other activities to collect and analyze safety data in that a formal request has been submitted by CHPA to FDA for MedWatch reports with fatal outcomes from FDA's AERS and SRS databases; at the time of this submission, these reports have not yet been received. This section also provides a review of safety data from prospective clinical trials in children (published and unpublished).

5.2 Maryland Poison Center (2004)

The BHD Petition makes general reference to reports from the Maryland Poison Center (MPC) during the year 2004 involving OTC cough and cold medication in children. Additional details were requested from the Maryland Poison Center and a summary of the information received from MPC is provided in this section.

During 2004, the MPC reported 18,575 calls for all substances involving children < 6 years of age; 1078 (5.8%) of these involved cough and cold products [Maryland Poison Center 2007]. Using the standard AAPCC reasons for exposure (Appendix 4, Table 5.1), almost all (99.2%) of the calls (1069 of 1078) about a cough and cold product involving children < 6 years of age were not related to a therapeutic dose; such exposures were classified as unintentional general [n=757 exposures] or therapeutic error [n=312 exposures].[1] The remaining eight calls (<1%) were classified as an adverse reaction occurring with normal, prescribed, labeled or recommended use.

Using the standard AAPCC coding for medical outcomes (Appendix 4, Table 5.2), 1062 of 1078 exposures (98.5%) did not result in outcomes considered to be of significant severity

[1] According to standard Poison Center coding conventions, exposures by curious young children who gain accidental and unsupervised access to medicines are coded as unintentional general and cases of unintentional deviation from a proper therapeutic regimen (wrong dose, wrong route of administration, wrong person, wrong substance) are coded therapeutic error.

(Appendix 4, Table 5.3). In the 16 remaining cases, 11 were unable to be followed but were judged as a potentially toxic exposure and five other that were followed developed symptoms consistent with an outcome of a moderate effect. No major effects or deaths were reported. For the five cases developing a moderate effect, available case information suggests several possible reasons for overdose of a cough and cold medicine (Table 5.4). Four of the cases involved accidental ingestions of adult medicines by curious young children. The fifth case did not involve an oral medication, but was the result of administration of nose drops to an infant. All five children had complete resolution of symptoms.

Table 5.4 Maryland PC Cases (n=5) With a Moderate Effect Involving Cough and Cold Product In Children <6 Years of Age (2004)

Available Case Descriptions	Possible Reasons for Overdose
1-year-old was unintentionally exposed at home to an adult product containing acetaminophen and diphenhydramine. Within 10 minutes of the exposure the child was referred to the emergency department (ED). In the ED tremor, muscle twitching and a heart rate (HR) = 190 beats/min were noted. Treatment consisted of activated charcoal and oral N-acetylcysteine (NAC). Symptoms resolved within six hours. The child was discharged after completion of a three-day course of NAC therapy.	Inadequate poison prevention at home Ingestion of an adult medicine by a child
23-month-old was unintentionally exposed at home to an adult prescription cough syrup that contained chlorpheniramine and hydrocodone as well as an unidentified decongestant. The PC was contacted when the child became sleepy and had "jerky" movements. In the ED the child had a HR =137 beats/min, a blood pressure (BP) = 148/82 mmHg and a respiratory rate = 30 breath/min. Following 2 hrs of observation, the child had normal HR and BP, was awake and alert, and was discharged.	Inadequate poison prevention at home Ingestion of an adult medicine by a child
13-month-old was unintentionally exposed to an unknown number of diphenhydramine tablets. Several hours after the ingestion, the child became twitchy and agitated and was taken to the ED. In the ED the child was agitated, irritable and appeared to grab at things that weren't there. No treatments were administered and after several hours of observation the child was discharged although still slightly agitated. The agitation improved overnight and the child was well the next day.	Inadequate poison prevention at home Ingestion of an adult medicine by a child
3-year-old ingested approximately 2.5 ounces of an OTC syrup containing pseudoephedrine hydrochloride 15 mg/5 mL along with an unidentified antihistamine at home. In the ED a BP = 137/87 mmHg was noted but the child was otherwise well. Activated charcoal was administered. Within six hours of presentation to the ED the child was asymptomatic and discharged.	Inadequate poison prevention at home Ingestion of overdose amount
4-month-old was administered a dose of phenylephrine hydrochloride 0.125% nose drops by his mother to treat congestion. Soon after receiving the medication, the child reportedly became tremulous, developed grunting/difficulty breathing, and the feet and legs became "a little blue". Upon arrival in the ED there was no evidence of tremor or cyanosis. The HR was 170-190 beats/min with a systolic BP = 166 mmHg. An EKG was demonstrated tachycardia. The child was observed and discharged within eight hours.	Dosing information of OTC product in child < 2 years of age is not provided for on OTC label.

5.3 American Association of Poison Control Centers (AAPCC)

At the request of CHPA, AAPCC searched the National Poisoning Data System [NPDS, which was formerly Toxic Exposure Surveillance System (TESS)] for the time period of January 1, 2000 through June 30, 2007 for all applicable contacts, exposures and cases in children less than 12 years of age for products containing at least one or more prescription or OTC cough and cold ingredient (Appendix 5, Table 5.5). This section provides findings for the most frequently used OTC cough and cold ingredients, including brompheniramine, chlorpheniramine, diphenhydramine, dextromethorphan, doxylamine, guaifenesin, phenylephrine, and pseudoephedrine.

AAPCC is a not-for-profit nongovernmental association representing the United States' poison centers (PCs) serving all 50 states. Poison centers use a standard data collection form and follow established national procedures and definitions for data collection. An exposure does not necessarily represent a poisoning, overdose, or adverse reaction. Since some exposures may go unreported to PCs the data referenced from NPDS does not represent the true incidence of national exposures to any substance(s). The objectives of analyzing the AAPPC data from NPDS are to identify characteristics of the exposures to prescription and OTC cough and cold medications in children, to obtain case level data for fatal cases for review by an independent medical expert panel and to gain information to identify root causes.

Over the 6.5 year time period of this search of the NPDS, a total of 774,960 poison center contacts, exposures or cases were recorded for prescription and OTC cough and cold medications in children <12 years of age; 99% of these exposures occurred at home or at another residence. The most frequently recorded cough and cold ingredient categories were decongestants (48%), antihistamines (42%), antitussive (32%) and expectorant (9%).

Using AAPCC standard coding conventions (Appendix 4, Table 5.2), 97.3% of cases did not result in outcomes considered to be of significant severity as follows: not followed, minimal clinical effects possible (44.1%), no effect (29.3%), not followed, judged as a nontoxic situation (11.9%), minor effect (10.6%), unrelated effect (1%), or confirmed nonexposure (0.37%). The remaining cases (<3%) were coded as follows: unable to follow, judged as potentially toxic (1.7%), moderate effect (0.86%), major effect (0.04%), or death (0.0045%).

The majority (62%) of AAPCC cases were reported in children 2 to < 6 years of age, followed by 28% of exposures in children < 2 years of age. This age distribution is not unexpected since accidental exposures and overdoses by curious young children (2 to < 6

years of age) who gain accidental and unsupervised access are particularly common for virtually all OTC and prescription medicines within the AAPCC database [Lai 2006]. A small proportion of cases (11%) involved cases in children 6 to <12 years of age.

AAPCC uses standard coding conventions to record reasons contributing to the occurrence of medication exposures. In this dataset, it is estimated that approximately 35% of contacts, exposures or cases had a reason coded. Table 5.6 provides a summary of some of the AAPCC coded reasons contributing to exposures of cough and cold medicines in various pediatric age groups. The frequency of reasons is cumulative across a specific reason category (e.g. product stored inappropriately), but not within a specific age group.

Table 5.6 AAPCC Reasons For Exposures to Cough and Cold Medications In Children <12 years (y) of Age (2000-2007)

Reasons for Medication Exposure	0 to <2 y N (%)	2 to <6 y N (%)	6 to <12 y N (%)
Inadequate Measures To Keep Medicines Out of the Reach of Children			
Product stored inappropriately[a]	1422 (28.43%)	3465 (69.29%)	114 (2.28%)
Accessed medication in purse or suitcase	628 (27.78%)	1594 (70.50%)	39 (1.72%)
Product temporarily open	1586 (29.31%)	3677 (67.95%)	148 (2.74%)
Therapeutic/Medication Errors			
Other incorrect dose	14447 (31.24%)	22736 (49.16%)	9065 (19.6%)
Confused units of measure	4922 (32.03%)	7486 (48.72%)	2957 (19.25%)
More than one product containing same ingredient	2943 (23.52%)	6057 (48.41%)	3513 (28.07%)
Health professional iatrogenic	610 (64.08%)	249 (26.16%)	93 (9.77%)
Ten-fold Dosing Error	633 (70.81%)	195 (21.81%)	66 (7.38%)
Dispensing Cup Error	3867 (30.39%)	6337 (49.8%)	2522 (19.82%)
Incorrect Form Concentration Given and Dispensed	6325 (34.20%)	8549 (46.22%)	3621 (19.58%)

a. The frequency of reasons is cumulative across a specific reason category (e.g. product stored inappropriately), but not within a specific age group (e.g. 0 to <2 years of age).

AAPCC data shows that ten-fold dosing errors and health professional iatrogenic errors were more common in the children under 2 years of age compared to such errors in the other age groups. These findings may be related to the lack of dosing information for children under 2 years of age on the OTC label of cough and cold products, whereas, reasons related to inadequate poison prevention were more common in children 2 to <6 years of age compared to the other age groups. These findings highlight that medication exposures and overdoses appear to occur in situations in which cough and cold products are not kept out of the reach of young children, are stored inappropriately in the home, are left as open containers and children gain unsupervised access to purses and suitcases.

Over the 6.5 year time period of these AAPCC data, a total of thirty-five exposures to a cough and cold medication in children were reported with a fatal outcome. Table 5.7 provides a summary of AAPCC coded reasons contributing to fatal exposures involving cough and cold medicines in various pediatric age groups.

Table 5.7 AAPCC Reasons For Fatal Exposures to Cough and Cold Medications In Children <12 years (y) of Age (2000-2007)

Reasons for Medication Exposure	0 to <2 y (N=20)	2 to <6 y (N=12)	6 to <12 y (N=3)	0 to < 12 y (Total N=35)
Adverse Reaction	2	0	2	4 (12%)
Intentional Misuse	1	0	0	1 (2%)
Malicious	5	1	0	6 (17%)
Therapeutic Error	3	4	0	7 (20%)
Unintentional General	4	6	0	10 (29%)
Unknown reason	5	1	1	7 (20%)

Among the several reasons for fatal overdose in children under 2 years of age is an important finding of malicious intent (i.e. AAPCC definition: patients who are a victim of another person intent to harm them); this is almost exclusively found in children under 2 years of age compared to the other age groups.

The distribution of the fatal outcome cases by age suggest that children under 2 years of age, and especially under age one year, may be at risk for inadvertent overdose. Detailed information about the actual root causes is often missing for cases where parents truly made unintentional errors while trying to use products for intended therapeutic uses. It is unclear whether infants are more or less likely to have serious morbidity from a specific overdose, but that there are more cases of fatal overdoses in this age range is clear.

Overall, AAPCC findings of reasons leading to exposures of cough and cold medicines in young children (< 2 years of age) are consistent with findings from two published reports by the Centers for Disease Controls (CDC). The CDC analyzed 2001 – 2003 data for nonfatal, unintentional medication exposures in children ≤ 4 years of age to prescription and OTC medications from hospital emergency department (ED) visits [CDC 2006]. OTC medicines were involved in 42.2 % of all exposures. An estimated 72% of all exposures were in children aged 1-2 years and majority of the cases occurred in homes. Across all children, the most common sources of medication exposures were pills left out or pill bottles left open. Other incidents involved medications administered in error by parents or caregivers and children opening pill boxes or purses.

In its second report, the CDC and the National Association of Medical Examiners (NAME) described three infants aged < 6 months found dead in their home during 2005 in which prescription and OTC cough and cold medications were determined by medical examiners or coroners to be the underlying cause [CDC 2007}. On autopsy, two cases had evidence of respiratory failure; no abnormalities of cardiac pathology were revealed in any of the infants. The post-mortem pseudoephedrine blood levels (4,743, 6,832 and 7,100 ng/mL) in these infants were approximately 9 to 14 times the levels expected from administration of recommended doses to children 2 to12 years of age. Table 5.8 provides the reported case information.

Table 5.8 CDC and NAME Survey - Case Descriptions [CDC 2007]

Available Case Descriptions	Possible Reasons for Overdose
A one-month male received a prescription medication containing pseudoephedrine (PSE), dextromethorphan and carbinoxamine; underlying cause of death was pseudoephedrine intoxication; significant medical conditions or contributing factors included interstitial pneumonia and recent hospitalization for fever.	Ingestion of an adult prescription medicine by an infant
A six month old female received a prescription medication containing pseudoephedrine, dextromethorphan and carbinoxamine plus an OTC medication containing pseudoephedrine and acetaminophen; underlying cause of death was pseudoephedrine and dextromethorphan intoxication; autopsy showed bronchopneumonia and empyema.	Administration of two medicines containing the same active ingredient at the same time
A three month old male received an OTC medication containing pseudoephedrine and acetaminophen; post-mortem blood levels also found doxylamine and dextromethorphan; significant medical conditions or contributing factors included the infant was found lying in crib in a prone position, a reported history of colic, born preterm (33 weeks) and a small fracture of left distal tibia; acute anoxic encephalopathy on autopsy.	Suspicious circumstances

5.4 Safety Data From Prospective Clinical Trials in Children

This section provides a summary of safety findings from prospective clinical trials and post-marketing safety studies in children <12 years of age for single ingredient and combination OTC cough and cold products. Appendix 5, Table 5.9 provides a detailed listing of each study including design, methods, sample sizes, treatments, subjects and safety findings. Overall, the reported adverse events were of mild to moderate severity. The adverse events recorded were as expected based upon the mechanism and pharmacology for each ingredient. There was a single pseudoephedrine exposure in a 22-month female from a post marketing surveillance study that reported a seizure whose causality was considered remote.

The OTC cough and cold ingredients varied in terms of number of clinical studies conducted and subjects exposed. In prospective clinical studies, pseudoephedrine had the largest number of exposures (n=1141 subjects), which was followed by chlorpheniramine (n=450 subjects), dextromethorphan (n=231 subjects) and brompheniramine (n=230 subjects). The other OTC cough and cold ingredients had a

limited number of subject exposures. There is limited safety data from these clinical trials in pediatric age subsets of <2 years. In conclusion, safety data findings from prospective clinical trials support that recommended doses of over-the-counter (OTC) cough and cold medicines are well tolerated in children.

5.5 Summary

- Safety data findings from prospective clinical trials support that recommended doses of over-the-counter (OTC) cough and cold medicines are well tolerated in children.
- Given the extensive use of pediatric OTC cough and cold products, reports with major effects and fatal outcomes are rare. The limited number of fatalities that have been reported, are mostly in children <2 years of age, resulting from caregivers administering supratherapeutic doses of these medicine or secondary to accidental overdoses following ingestion of these products by curious young children who gain accidental and unsupervised access.
- In children <6 years of age, inadequate poison prevention in the home (inadequate measures to keep medicines out of the reach of children) leads to a significant number of accidental exposures. Despite this, overdoses resulting in toxicity and requiring healthcare evaluation and treatment are rare.
- Collectively, data from various sources suggest that medications errors with OTC cough and cold products in children may lead to unintentional overdose when:
    - Products are administered without using an appropriate measuring device
    - Confusion occurs between different product forms and varying concentrations
    - Multiple products containing the same or similar active ingredients are administered at the same time
    - Adult products are administered to children.
    - Healthcare providers provide inaccurate instructions or caregivers misunderstand their instructions, especially in children < 2 years of age.
    - OTC cough and cold products are given for unlabeled uses (e.g. sedation) that may contribute to overdose.
- CHPA and its member companies are continuing a number of activities to collect and analyze safety data.

6 INSIGHTS ON PARENTS, CAREGIVERS, AND HEALTHCARE PROFESSIONALS

6.1 Key Findings

- The experience of parents and caregivers, especially when they have multiple children, plays a key role in determining whether they ask a healthcare professional for advice about administering an OTC cough and cold medicine to their children.
- Parents and caregivers have very little understanding about active ingredients and rarely ever look at that section of the label.
- Parents and caregivers do not report difficulty successfully using dosing devices when administering OTC cough and cold medicines to their children.
- Healthcare professionals are reluctant to recommend OTC cough and cold medicines to children under 2 years of age.
- Healthcare professionals are more likely to recommend OTC cough and cold medicines to children 2 years of age and older.
- Parents and caregivers likely would not administer any medication to their children if it were labeled “do not use.”

6.2 Parents and Other Caregivers

CHPA commissioned a qualitative survey during the summer of 2007 to gain a better understanding of how parents and other caregivers perceive OTC cough and cold medicines for their children, how they administer these medications to children, the type of communication they have with pediatricians and other healthcare professionals regarding use, and if there are gaps to general safe use [West Mill Marketing 2007]. The survey consisted of 66 in-depth caregiver interviews. All interviewees were caregivers of children 6 years of age or younger and had previously administered OTC cough and cold medicines to the child(ren) in their charge. Sixteen respondents cared for children under 6 months of age, 29 respondents cared for children 6 months to 2 years of age, and 28 respondents cared for children 2 years to 6 years of age. Some respondents had more than one child within the age ranges. The interviews were conducted in Edison, New Jersey, and Kansas City, Missouri. Respondents included 46 mothers, 11 fathers, and nine caregivers (other than mothers or fathers). The respondents were from a mix of ethnic backgrounds: 30 were Caucasian, 13 African-American, 16 Hispanic, and 7 Asian. Education and household income varied.

Below is a summary and analysis of these findings. CHPA additionally is conducting a quantitative study (fielded September 13, 2007) which will be presented at the FDA advisory committee meeting on October 18, 2007.

6.3 Overview of Findings from Parents and Other Caregivers

The overwhelming reason cited by respondents for giving OTC cough and cold medications to their children was to help their children feel better. Almost all study respondents described themselves as generally comfortable administering these medicines to their children under 6 years old. While education level, income level, or ethnic background did not have an impact on a respondent's adherence to the recommended administration of OTC cough and cold medicines or attitude toward asking a healthcare professional for assistance, two influencing factors did emerge:

1. Perception of OTC medicines as either "serious" medications or as "safe" medications, and
2. Experience of the caregiver generally related to the number of children in the household. Those with more than one child in the household stated that they did not need to talk to a doctor when they could rely on their memory from previous experiences to determine a child's dose.

A majority of respondents admitted to reading only portions of the Drug Facts label.

- Almost all reported reviewing the front of a medicine package (for the product name or brand family, the symptoms the medicine treats, and package graphics that would tend to indicate if the medicine is appropriate for young children).
- Almost all reviewed the dosing directions. Respondents overwhelmingly said the dosing directions were clear and easy to find.
- A smaller number also reviewed the warnings section.
- All respondents recalled seeing "ask a doctor" on medications, but most did not have an understanding of why "ask a doctor" would be on a label rather than specific dosing instructions.
- **Almost all respondents indicated that they would not administer any medication to their child if it were labeled "do not use."**

This qualitative study also highlighted consumers' lack of understanding about active ingredients. A medication's active ingredient(s) played a negligible part in the selection

process; rather, respondents based their selection decisions on the child's symptoms; brand names; and recommendations of pediatricians, family, and friends.

This lack of understanding about active ingredients was underscored when respondents were questioned about the concomitant administration of multiple medications.

- Most were reluctant to dose their children with two different medications at the same time. However, a small minority, viewing OTCs as "safe," expressed very little concern about dosing with multiple medications.
- Almost all said they would first ask their doctor or pharmacist for advice before administering multiple medications to their children. Many voiced concerns over the potential for overdose when dosing with two medications containing the same active ingredient. Others guessed that the two medicines with the same active ingredient would be compatible.

This study did not uncover any physical obstacles to the actual administration of OTC cough and cold medicine to children. Most caregivers reported using the dosing device provided with a medication and were fully confident in their abilities to accurately administer the correct amount of a particular medication.

- Almost all respondents reported having other dosing devices on hand in case none were supplied with the particular OTC medication.
- The majority of study respondents did not express difficulty maintaining a dosing schedule for their child, even when multiple caregivers are involved.

This qualitative study found the following results when caregivers were asked how much medicine to give a child, or how frequently to administer the medication:

- **59% of respondents indicated they would ask a healthcare professional for help.** These caregivers typically expressed an appreciation of getting the dose correct and reported having access to 24-hour healthcare services, such as a doctor's office, nurse helpline, or pharmacy.
- **27% indicated they would be more likely to make their own decisions** without contacting a healthcare professional. This group was hesitant to bother their doctor, didn't want to wait for a return phone call from a healthcare professional, or felt that OTC medicines are safe enough that they didn't need to be concerned with exact dosing recommendations. This group also relied heavily on advice from friends or relatives, and, in some cases, used dosing instructions for one medication as the correct dose for a different medication.

- **14% of respondents indicated that they would likely contact a healthcare professional only during regular business hours**, expressing reticence towards interrupting a busy pharmacist or trying to contact a healthcare professional outside of business hours or if they were in a hurry to get a response.

When caregivers did not consult a healthcare professional, the following methods were most frequently cited as techniques used by this group to determine dosage:

- Using half of the lowest recommended dose on the label
- Using the lowest dose marked on the dosing device included with the medicine
- Using the same dose their doctor or pharmacist recommended to them for another medicine

When questioned about alternative therapies, the study found the following:

- Many study respondents used a humidifier to help treat a cold, and were generally satisfied with this method.
- A slight majority of the many respondents who reported having tried chest rubs were satisfied, citing messiness as a reason for dissatisfaction.
- Less than half of the respondents used a saline nose spray for mucus removal; most of these respondents, however, were satisfied, but some indicated that sprays were difficult to use with young children.
- Most study respondents had not tried either menthol or eucalyptus room fresheners or herbal bathing salts for treating a cough or cold symptoms.

6.4 Healthcare Professionals

CHPA and its member companies have used a number of research tools to better understand the perceptions and uses of OTC cough and cold medicines among pediatricians and other healthcare providers. In particular, these findings show a high level of comfort among pediatricians with these products in children ages 2 years and above. There is less of a comfort level and somewhat of a reluctance to recommend these medicines for children under 2 years of age and especially for children under 9 months of age [West Mill Marketing 2007]. Research also shows that pediatricians stand out as the key sources of information and advice about medications for children under the age of 2 years [Proprietary data from Weinman Schnee Morais Inc. 2007].

6.5 Overview of Findings from Healthcare Professionals

Healthcare professionals, including physicians and pharmacists in this report, cite a high-degree of communication with parents, especially new parents, regarding OTC cough and cold medicines for children.

- The majority exercise caution regarding whether to recommend an OTC cough and cold medication for a child, most reporting caution or reluctance to recommend these medications for children under the age of 2 years. The majority do recommend OTC cough and cold medicines for children over the age of 2 years.
- Almost all physicians cited a paucity of guidelines for recommending the use of OTC cough and cold medicines for their young patients.
- Healthcare professionals also reported a lack of awareness of active ingredients in OTC cough and cold medicines among parents.
- Healthcare providers see the key benefits of cough and cold medications as symptom relief followed by a good night's sleep [Proprietary data from Market Tools/Healthcare 2007].

Three hundred healthcare professionals surveyed expressed the following attitudes about recommended courses of treatment for children with a cough and/or cold:

- Most say they are generally cautious with children under the age of 2 years of age, and some say they are more cautious with children under the age of 12 months.

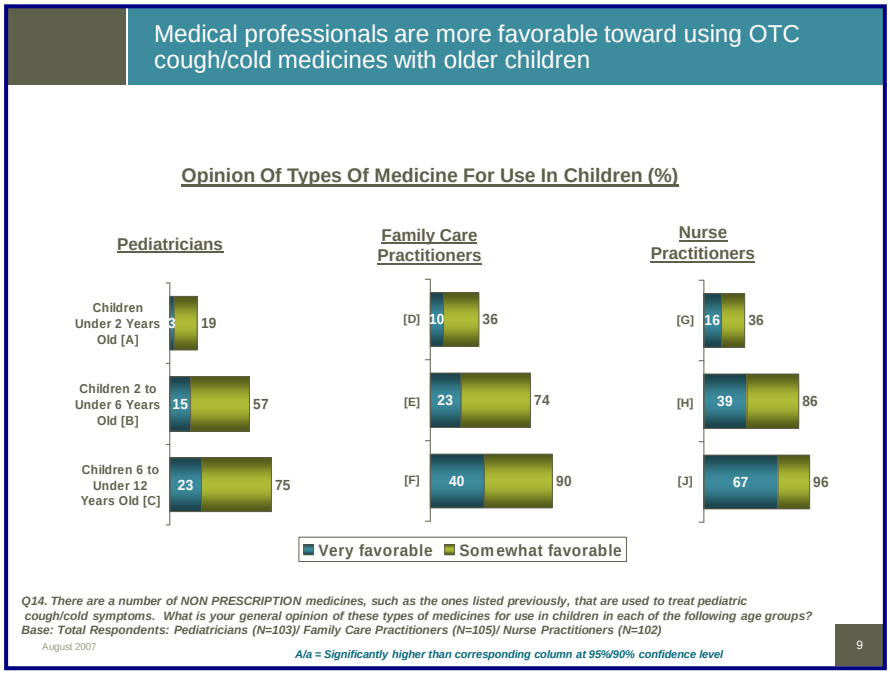
- The majority of respondents say that they are more comfortable and less cautious recommending OTC cough and cold medicines to children once they are past the age of 2 years.

Healthcare professionals recognize that experience is an important determinant of whether caregivers seek out their advice when it comes to OTC cough and cold medicines.

- Most study respondents indicate that new parents are the most cautious and ask for help with the use of an OTC cough or cold medicine.
- Experienced parents (those with more than one child) rely more on their own experience to make decisions.
- Most physician respondents feel that they have the most influence with the use of an OTC cough and cold medicine with their patients who are under 6 months of age.
- The majority of physician and pharmacist respondents say that they do not have a great concern about the difficulty patients or customers might have using the dosing devices that come with OTC cough and cold medicines.

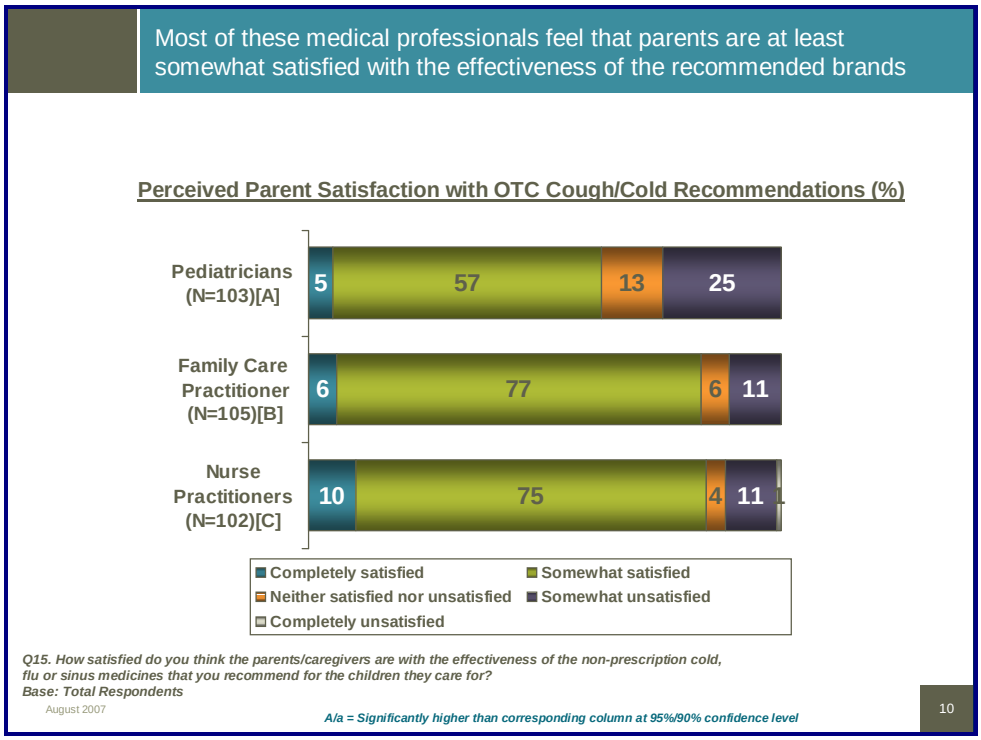
Almost all physicians say that they have no real guidelines for recommending the use of OTC cough or cold medicines for their young patients. They rely on their experience. When required to recommend dosing, respondents mentioned several methods:

- Cutting the dose that is included on the package label (usually by ½ of the label dose, or sometimes by ¼ of the label dose for younger or smaller (weight) children)



[Proprietary data from Market Tools/Healthcare 2007]

- Referencing product ingredients in the *Pediatric Dosing Handbook* or the *Facts and Comparison* reference book to calculate dosing
- Some pharmacists say they rely on memory of what doses pediatricians have recommended in the past.



[Proprietary data from Market Tools/Healthcare 2007]

6.6 Conclusions

Qualitative research conducted with parents, other caregivers, and healthcare professionals, underscores the lack of understanding about active ingredients by parents and other caregivers. While generally familiar with the front of OTC cough and cold medicine packages and with the Drug Facts label, this important segment of consumers reads only portions of the label, namely, the symptoms the medicine treats, the dosing directions, and, sometimes, the warnings. Parents and other caregivers rely on the advice of physicians, pharmacists, relatives, and friends when they have questions about OTC cough and cold medicine dosing for their children. Parents and other caregivers, however, do not report any particular questions or difficulties with dosing devices or dosing schedules.

Investigation into the habits of parents and other caregivers, and into the perceptions of healthcare professionals, point to a number of conclusions:

- Parents and other caregivers are motivated by a sincere desire to make their children feel better when suffering from cough and cold symptoms, and are therefore ripe for educational efforts.

- Parents and other caregivers need additional educational efforts to explain the importance of paying attention to active ingredients.

- Parents and other caregivers rely upon healthcare professionals for advice regarding OTC cough and cold medications for children. Healthcare professionals must be integrated into any systematic, industry-wide effort that involves the changing of OTC cough and cold medications' labels for children under the age of 2 years.

7 RECOMMENDED ACTION PLAN

7.1 Key Points

CHPA and its member companies recommend the following steps to promote appropriate use of OTC cough and cold medicines in children:

- A risk minimization plan to help reduce overdose and misuse of OTC cough and cold medicines, which includes proposed label recommendations, educational initiatives, and observational studies. The proposed label recommendations include:
    - Changing “Ask a doctor” to “Do Not Use” in children under 2 years of age
    - Adding “Do not use to sedate children” or similar language for monograph antihistamines
- A pediatric research program of pharmacokinetic studies in children 2 to under 12 years of age to confirm or refine recommended doses.

7.2 *Risk Minimization Plan*

While the available data supports that recommended doses of OTC cough and cold medicines are well tolerated in children, rare adverse events, including death, have been reportedly associated with the overdose and misuse of these medicines, especially in young children. To address overdose and misuse of these medicines, a comprehensive risk minimization plan is proposed. This plan includes the following components:

- Specific label changes that pertain to young populations, including:
    - “Do not use” in children under 2 years of age
    - Language on monograph antihistamines to indicate “Do not use to sedate children”
- A multi-year, national education campaign to reinforce the importance of following OTC label directions and to enhance ongoing efforts to reduce overdose and misuse in children
- Prospective safety study to reaffirm the safety of OTC cough and cold medicines at recommended doses

7.2.1 Overview

The root causes of deaths and serious adverse events reportedly associated with the use of OTC cough and cold medicines in children are still under review, but several high risk scenarios and behaviors are apparent:

- Overdose and misuse in children less than 2 years of age
- Unintentional accidental exposure by curious young children (inadequate measures to keep medicines out of reach of children)
- Use of medicines for unlabeled indications, especially sedation
- Use of medicines intended for adults in children
- Use of multiple medicines containing the same or similar ingredients at the same time

When used inappropriately, OTC cough and cold products can pose risks, especially to young children under 2 years of age. Label changes along with strong educational programs directed at both consumers and healthcare professionals can help reduce this risk. CHPA is committed to addressing the main concerns discussed above. We have outlined the following goals that seek to reduce overdose due to misuse and unintentional accidental exposure:

7.2.2 Goals

1. Caregivers use OTC cough and cold medicines only for labeled indications and only in recommended doses.
2. OTC cough and cold medicines are only used in the age range for which they are indicated.
3. Adult products are not used in children.
4. Caregivers do not use OTC cough and cold medicines in children younger than 2 years of age.
5. OTC monograph antihistamines are not used to sedate children.
6. Caregivers do not use multiple medications with the same or similar active ingredients in children at the same time.
7. Medicines are kept out of the reach of children.

CHPA and its members will address these goals through proposed label changes and an aggressive national education campaign.

7.2.3 Proposed Label Recommendations

CHPA and its members recommend enacting strong label changes on OTC cough and cold medicines to help reduce overdose and misuse. Our highest priority is continuing to provide caregivers with all the information necessary to use these medicines appropriately.

CHPA and its members recommend that dosing directions on OTC cough and cold medicines for children 0 to under 2 years of age be changed from “ask a doctor” or “consult a physician” to read “Do Not Use.” The spirit of “ask a doctor” was to encourage parents and other caregivers to discuss symptoms, as well as dosing recommendations, with a healthcare provider. Cases of overdose and misuse associated with pediatric OTC cough and cold medicines have been reported. This label change is intended to help prevent consumer misuse and overdose. This label change should not be misunderstood to suggest that the appropriate use of these medicines at the specific direction of a healthcare provider is unsafe.

The following factors support these recommendations: the challenge of obtaining pharmacokinetic data in this age group; a proportionately higher number of fatal outcomes from overdose in children under 2 years of age; and the absence of dosing information in the OTC monograph and on the label.

Additionally, adverse events have been reported related to caregivers administering monograph antihistamines for sedation of children. As this is not an indication for use of these ingredients in children, CHPA and its members strongly recommend adopting language on the label warning caregivers not to use these medicatines for sedation.

These label changes are important to communicate these key messages to parents, caregivers, and healthcare providers. In addition, these messages should be reinforced with a national education campaign targeting both consumer and healthcare professionals.

7.2.4 Education

CHPA is developing an industry-wide, multi-million dollar, multi-year national initiative to educate parents and other caregivers on the appropriate use of OTC medicines in children. The campaign will be conducted by CHPA’s nonprofit, educational foundation, the Consumer Health Education Center (CHEC).

This campaign will be inclusive in its efforts by enlisting the expertise of various national medical and consumer organizations and governmental agencies. The goals of the initiative will be:

- To educate consumers, particularly parents, about appropriate use of cough and cold medicines in children.
- To educate healthcare professionals about recommended label changes and to encourage healthcare professional/parental communication.
- To encourage parents to discuss children's symptoms with their healthcare providers

Of primary importance in the development of the CHEC campaign is the establishment of key partnerships with a broad range of organizations with diverse outreach in order to verify messaging and maximize reach through distribution channels. The partners in the campaign will create educational materials in hardcopy, electronically, and utilizing new or multi-media. In addition, appropriate pediatric dosing messages will be presented directly at tactical points in consumers' lives, such as in hospital maternity wards, pediatricians' offices, and at the point-of-purchase. The distribution of messages will be multiplied with a strategic use of media through earned media (news releases, press conference, notable spokesperson, media tours, etc.), paid advertising, and public service announcements. Moreover, CHEC will create mutual relationships with online health information providers to ensure visibility of the importance of appropriate pediatric dosing and the scientifically valid messages of the campaign.

7.2.5 Measurements

An important aspect of the risk minimization plan is the measurement of the impact of goals and objectives outlined above. To do this, CHPA will establish clearly defined tools and goals to measure the impact of these initiatives, including measuring both the attitudes and behaviors of caregivers and healthcare professionals prior to and throughout the lifecycle of this campaign, in addition to standard public relations metrics.

Additionally, CHPA will continue to work with the American Association of Poison Control Centers and its members to develop systems to better understand the behaviors around misuse.

7.2.6 Observational Study

CHPA member companies recommend conducting an observational study to be initiated by industry in 2008. The primary objective of this prospective study is to further confirm the safety profile of cough and cold ingredients at recommended doses. FDA advice on the methodology and protocol will be sought prior to commencement of the study.

7.3 Proposed Pediatric Research Program

As discussed in Section 4 of this document, pediatric pharmacokinetic (PK) data confirm that current pediatric OTC doses for pseudoephedrine and chlorpheniramine align with those doses showing efficacy in adults. While PK data in adults are available for all ingredients discussed herein, additional pediatric PK data can further confirm or refine doses for other ingredients. Therefore, CHPA member companies recommend and have begun discussions with FDA about the conduct of pharmacokinetic studies in children 2 to under 12 years of age for the following ingredients:

- Dextromethorphan
- Phenylephrine
- Guaifenesin
- Brompheniramine
- Diphenhydramine
- Doxylamine

The main objectives for the pediatric PK studies are:

- To determine whether maximum and total systemic drug exposures for current pediatric doses are comparable to those for adult doses
- To assess whether the dose-concentration relationship is age-dependent after adjustment for differences in body size

CHPA and its member companies are working expeditiously to identify research facilities that have the expertise and capacity to undertake pharmacokinetic studies in children. Our targeted timeframe for completing these studies and sharing the results with the agency is 12 to 24 months after the initiation of the studies.

7.3.1 Evaluation of Other Determinants

In parallel to conducting pediatric PK studies, we are committed to working in close cooperation with FDA and other experts to identify strategies to bridge efficacy data, including the development of validated, pediatric pharmacodynamic or clinical symptom endpoints.

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Appendix 1: Pharmacokinetic and Efficacy Summaries for Eight OTC Cough-Cold Ingredients

A 1-1. **Pharmacokinetic and Efficacy Summaries for OTC Brompheniramine**

1. Active Ingredient
   - Name of ingredient: Brompheniramine maleate
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	2 mg every 4-6 hr, not to exceed 12 mg in 24 hr	4 mg every 4-6 hr, not to exceed 24 mg in 24 hr	"Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

Brompheniramine maleate

Publication Reference & Study Characteristics	***Simons et al. 1999;*** Single-dose study in 14 children (age 9.5 ± 0.4 yr, weight 31.9 ± 1.7 kg); **syrup**	***Simons et al. 1982a;*** Single-dose study in 7 adults (age 28 ± 11 yr, weight 72.8 ± 13.5 kg); **syrup**
Results:	**Children 4 mg dose**	**Adults 9.8±1.7 mg dose**
AUC *(ng/mL/hr)*	127 ± 18	293 ± 32
tmax *(hr)*	3.2 ± 0.3	3.1 ± 1.1
Cmax *(ng/mL)*	7.7 ± 0.7	11.6 ± 3.0
Vd *(L/kg)*	20.0 ± 1.8	11.7 ± 3.1
t½ *(hr)*	12.4 ± 1.1	24.9 ± 9.3
Cl *(mL/min/kg)*	20.2 ± 2.1	6.0 ± 2.3

5. Efficacy Study Summaries for Brompheniramine

These summaries are from published randomized, placebo-controlled studies of brompheniramine alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Hutton et al. 1991	[see below]			
	Clemons et al. 1997	[see below]			
6 months - <6 years	Hutton et al. 1991	Double-blind placebo (n=27)-controlled trial of fixed combination (n=36) of brompheniramine, phenylephrine, & phenylpropanolamine in children (0.5-5 yr, mean 25 ± 15.7 months) with signs of upper respiratory infection (i.e., nasal congestion or rhinorrhea); also a "no treatment" group (n=33)	Fixed combination of brompheniramine maleate (4 mg/5 ml), phenylephrine HCl (5 mg/5 ml), & phenyl-propanolamine HCl (5 mg/5 ml) given 3 times/ day so that brompheniramine dosage was 0.5-0.75 mg/kg body weight/day for 2 days	Parents' subjective assessment of symptoms (congested or runny nose, breathing trouble, fever, cough, decreased appetite, crankiness, sleep disturbance, & excessive sleepiness) at 48 hr	No differences among groups in individual or composite symptom score changes
	Clemons et al. 1997	Double-blind placebo (n=31)-controlled trial of a combination (n=28) of brom-pheniramine & phenylpropanolamine in children (0.5-5 yr) with upper respiratory infections (<7 days' duration)	Combination of brom-pheniramine maleate (2 mg/5 ml) & phenyl-propanolamine HCl (12.5 mg/ml): 0.5 tsp for children 6 mo-2 yr & 1 tsp for those 2-5 yr, no more often than every 4 hr & no more than 4 doses, for 48 hr	Parents' subjective assessment 2 hr after each dosage of change in symptoms (runny nose, nasal congestion, & cough) & whether child was sleeping	No statistically significant differences in symptom improvement between groups, but higher proportion of treated children sleeping 2 hr after dosage
6 - <12 years	No studies available				

≥12 years & Adults	Gwaltney & Druce 1997	Double-blind placebo (n=112)-controlled trial of brompheniramine (n=113) in subjects with induced (rhinovirus type 16) colds	Brompheniramine maleate 12 mg 2 times/day for ≤4 days	Daily nasal secretion weights, 12-hr sneeze & cough counts; subjective symptom (sneezing, rhinorrhea, nasal obstruction, sore throat, cough, headache, malaise, chilliness) scoring and global evaluations	Lower nasal secretion weights, lower sneezing counts & severity scores, lower cough counts, lower total symptom scores with brompheniramine, which was efficacious for treating sneezing, rhinorrhea, & cough

A 1-2. **Pharmacokinetic and Efficacy Summaries for OTC Chlorpheniramine**

1. Active Ingredient
   - Name of ingredient: Chlorpheniramine maleate
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	2 mg every 4-6 hr, not to exceed 12 mg in 24 hr, "or as directed by a doctor."	4 mg every 4-6 hr, not to exceed 24 mg in 24 hr, "or as directed by a doctor."	"Children 2 to under 6 years of age: oral dosage is 1 milligram every 4 to 6 hours, not to exceed 6 milligrams in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

Chlorpheniramine maleate

Publication Reference & Study Characteristics	***Thompson et al. 1981;*** Single-dose study in 7 patients aged 6 – 14 yr (weight 24 - 36 kg); **intravenous solution**	***Simons et al. 1982b, Simons et al. 1984;*** Single-dose study in 11 patients aged 6 – 16 yr (mean age 10.95 ± 2.98 yr, weight 39.63 ± 9.19 kg); **syrup**	***Kotzan et al. 1982;*** Single-dose study in 15 healthy male volunteers aged 18 – 27 yr (mean age 21 yr, mean weight 74 kg); **syrup**	
Results:	**Children 0.1 mg/kg i.v. dose**	**Children 0.12 mg/kg** (corr. to mean dose of **4.8 mg** on basis of mean weight)	**Adults**	
			4 mg dose	**8 mg dose**
AUC *(ng/mL/hr)*	*not reported*	246 ± 125	65.4 ± 21.8	156.3 ± 60.7
t_{max} *(hr)*	*not reported*	2.5 ± 1.5	3.4 ± 2.5	3.8 ± 2.7
C_{max} *(ng/mL)*	*not reported*	13.5 ± 3.5	5.9 ± 2.3	11.3 ± 2.9
Vd *(L/kg)*	3.81 ± 1.46	7.0 ± 2.8	*not reported*	*not reported*
t½ *(hr)*	9.6 ± 3.6	13.1 ± 6.6	14.6 ± 3.4	17.3 ± 4.4
Cl *(mL/min/kg)*	5.38 ± 1.5	7.23 ± 3.16	*not reported*	*not reported*

5. Efficacy Study Summaries for Chlorpheniramine

These summaries are from published randomized, placebo-controlled studies of chlorpheniramine alone or in combination with other drug active ingredients and a meta-analysis of data from randomized, placebo-controlled studies.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Sakchainanont et al. 1990	[see below]			
1.5 months - <6 years	Sakchainanont et al. 1990	Double-blind placebo (n=47)-controlled trial of chlorpheniramine (n=48) and clemastine (n=48) in children 1.5-60 months old (mean 23±16.12) with rhinorrhea with or without occasional non-productive cough of 3 days' duration	Chlorpheniramine maleate 0.35/kg/day 3 times/day or clemastine fumarate 0.05 mg/kg/day 2 times/day for 3 days; medications and placebo each in equal volumes of 0.5ml/kg/dose	Subjective evaluation of symptoms (nasal discharge, nasal turbinate edema, cough)	Statistically significant improvement of every symptom in every group; no benefit of treatment shown except in children with copious nasal discharge; amount of nasal discharge reduced in 25/48 children with chlorpheniramine, 28/48 with clemastine, and 22/47 with placebo
6 - <12 years	No studies available				
≥12 years & Adults	Howard et al. 1979	Placebo (n=138)-controlled trial of chlorpheniramine (n=133) in subjects with signs & symptoms of common cold for 24-48 hr	Chlorpheniramine maleate 4 times/day (dose not specified) for 6 days	Subjective evaluation of symptoms by subjects (runny nose, stuffy nose, sneezing, postnasal drip, cough, watery eyes, & overall condition) & physicians (nasal swelling, redness, secretions, & obstruction & overall	Chlorpheniramine superior to placebo in lessening the degree of symptoms; statistically significant differences on 1st day & as late as the 7th day

				condition)	
	Crutcher & Kantner 1981	Double-blind placebo (n=54)-controlled trial of chlorpheniramine (n=52) in subjects (18-65 years old) with onset of a cold <48 hr	Chlorpheniramine maleate (marketed OTC product, presumably 4 mg) 4 times/ day for 7 days	Subjective evaluation of symptoms (runny stuffy nose, sneezing, postnasal drip, cough, & sore throat) by subjects & of signs (nasal swelling, redness, secretions, and nasal obstruction) by physicians	Chlorpheniramine significantly effective in relieving cold symptoms and showed a clear trend toward reducing signs of a cold
	Doyle et al. 1988	Double-blind placebo (n=18)-controlled trial of chlorpheniramine (n=19) in subjects (18-44 yr) with induced (rhinovirus type 39) colds	Chlorpheniramine (salt not specified) 4 mg every 4 hr (24 mg/day) for 5 days	Objective assessment of nasal patency (by rhinomanometry), eustachian tube function (by 9-step test & sonotubametry), middle ear pressure (by tympanometry), & nasal clearance (by dyed-saccharin technique); nasal secretions quantified; objective evaluations of symptoms (malaise, rhinorrhea, sneezing, and nasal congestion) by subjects	Chlorpheniramine effective in decreasing sneezing and nasal secretions and in increasing mucociliary clearance; no difference between groups in objective measures of nasal congestion or response of middle ear & eustachian tube
	Gaffey et al. 1987	Double-blind placebo (n=11)-controlled trial of chlorpheniramine (n=10) in subjects with induced (rhinovirus type 29) colds	Chlorpheniramine maleate 4 mg 4 times/day (16 mg) for 4 days	Expelled nasal mucus weight measured & used nasal tissues counted; clinical symptoms monitored to determine frequency & severity of clinical illness	Chlorpheniramine not shown to have a significant effect on nasal symptoms or nasal mucus production

	Gwaltney et al. 2002	Double-blind placebo (n=30) controlled trial of a combination (n=61) of chlorpheniramine & ibuprofen [against a combination (n=59) of intranasal interferon (IFN)-α2b + chlorpheniramine + ibuprofen] in subjects 18-51 years old) with induced (rhinovirus type 39) colds	Chlorpheniramine maleate 12-mg sustained-release tablet + ibuprofen 400 mg every 12 hr for 4.5 days (with or without concomitant intranasal administration of IFN-α2b 6 x 10^6 U 3 times)	Nasal mucus weight determined for 24-hr periods; symptom (sneezing, runny nose, nasal obstruction, sore throat, cough, headache, malaise, & chilliness) data collected daily	Reduction in severity of rhinorrhea, sneezing, nasal obstruction, sore throat, cough, & headache & in nasal mucus production, & nasal tissue use with treatment; enhanced effectiveness with concomitant administration of IFN-α2b
	D'Agostino et al. 1998	Meta-analysis of raw data from 8 double-blind studies (placebo-controlled), including 3 on chlorpheniramine, to evaluate effectiveness of antihistamines to reduce symptoms of runny nose & sneezing over the first 2 days of medication for subjects having common colds for 24-48 hr	Chlorpheniramine at 4 mg 4 times/day	Statistical analysis of data on severity of runny nose & sneezing	Homogeneity of treatment effect across studies & consistency confirmed for pooling the studies; antihistamines shown to be statistically significantly more effective than placebo in reducing severity of runny nose and sneezing

A 1-3. **Pharmacokinetic and Efficacy Summaries for OTC Diphenhydramine**

1. Active Ingredient
   - Name of ingredient: Diphenhydramine citrate; diphenhydramine hydrochloride
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	*For products containing diphenhydramine citrate:* 19-38 mg every 4-6 hr, not to exceed 228 mg in 24 hr *For products containing diphenhydramine hydrochloride:* 12.5-25 mg every 4-6 hr, not to exceed 150 mg in 24 hr	*For products containing diphenhydramine citrate:* 38-76 mg every 4-6 hr, not to exceed 456 mg in 24 hr *For products containing diphenhydramine hydrochloride:* 25-50 mg every 4-6 hr, not to exceed 300 mg in 24 hr	*For products containing diphenhydramine citrate:* "Children 2 to under 6 years of age: oral dosage is 9.5 milligrams every 4 to 6 hours, not to exceed 57 milligrams in 24 hours." *For products containing diphenhydramine hydro-chloride:* "Children 2 to under 6 years of age: oral dosage is 6.25 milligrams every 4 to 6 hours, not to exceed 37.5 mg in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

Diphenhydramine hydrochloride

Publication Reference & Study Characteristics	***Simons et al. 1990;*** Single-dose study in 21 subjects divided into 3 groups: **syrup** - children (age 8.9 ± 1.7 yr, weight 31.6 ± 6.8 kg) - young adults (age 31.5 ± 10.4 yr, weight 70.3 ± 9.9 kg) - elderly adults (age 69.4 ± 4.3 yr, weight 71.0 ± 11.4 kg)		
Results:	**Children 39.5±8.4 mg dose**	**Young Adults 87.9±12.4 mg dose**	**Elderly Adults 86.0±7.3 mg dose**
AUC *(ng/mL/hr)*	475 ± 137	1031 ± 437	1902 ± 572
tmax *(hr)*	1.3 ± 0.5	1.7 ± 1.0	1.7 ± 0.8
Cmax *(ng/mL)*	81.8 ± 30.2	133.2 ± 37.6	188.4 ± 54.5
Vd *(L/kg)*	17.9 ± 5.9	14.6 ± 4.0	10.2 ± 3.0
t½ *(hr)*	5.4 ± 1.8	9.2 ± 2.5	13.5 ± 4.2
Cl *(mL/min/kg)*	49.2 ± 22.8	23.3 ± 9.4	11.7 ± 3.1

5. Efficacy Study Summaries for Diphenhydramine

These summaries are from published randomized, placebo-controlled studies of diphenhydramine alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	No studies available				
2 - <6 years	Paul et al. 2004	[see below]			
2 – 16.5 years	Paul et al. 2004; Yoder et al. 2006	Double-blind placebo (n=34)-controlled trial of diphenhydramine (n=33) & of dextromethorphan (n=33) in children (2-16.5 yr, median 4.50 yr) with nocturnal cough associated with upper respiratory infection (average illness duration = 4.21±1.57 days before treatment)	Diphenhydramine (salt not specified, but most likely hydrochloride) at 1.25 mg/kg body weight as a single dose 30 minutes before bedtime	Parents' subjective assessment of frequency, severity, & bothersome nature of nocturnal cough of sleep quality for child & parents; also subjective assess-ments by subsets (n=12 for diphen-hydramine; n=13 for placebo) of children (6.2-16.5 yr, median 7.5 yr)	Improvement for all outcomes for all groups; diphenhydramine not superior to placebo in providing nocturnal symptom relief
> 12 years & Adults	Paul et al. 2004; Yoder et al. 2006	[see above]			

A 1-4. **Pharmacokinetic and Efficacy Summaries for OTC Doxylamine**

1. Active Ingredient
   - Name of ingredient: Doxylamine succinate
   - Pharmacotherapeutic class: Antihistamine

2. Indication According to OTC Monograph
   Either "Temporarily" (any one of the following: "relieves," "alleviates," "decreases," "reduces," or "dries") "runny nose and" (any one of the following: "relieves," "alleviates," "decreases," or "reduces") "sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever" or "For the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever." May be followed by one or both of the following: "or other upper respiratory allergies" or "(allergic rhinitis)."

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	"Consult a doctor"	3.75-6.25 mg every 4-6 hr, not to exceed 37.5 mg in 24 hr	7.5-12.5 mg every 4-6 hr, not to exceed 75 mg in 24 hr	"Children 2 to under 6 years of age: oral dosage is 1.9 to 3.125 milligrams every 4 to 6 hours, not to exceed 18.75 milligrams in 24 hours."	"May cause excitability especially in children." *For products labeled only for use by children under 12 years of age:* "May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do not give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor." "Do not give this product to children who have a breathing problem such as chronic bronchitis, or who have glaucoma, without first consulting the child's doctor."

4. Pharmacokinetic Characteristics

No data from pediatric pharmacokinetic studies are available.

5. Efficacy Study Summaries for Doxylamine

These summaries are from published randomized, placebo-controlled studies of doxylamine alone or in combination with other drug active ingredients and a meta-analysis of data from randomized, placebo-controlled studies.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	No studies available				
2 - <6 years	No studies available				
6 - <12 years	No studies available				
> 12 years & Adults	Eccles et al. 1995	Double-blind placebo (n=343)-controlled trial of doxylamine (n=345) in subjects (mean age 25 yr) with colds	Doxylamine succinate 7.5 mg 4 times/day up to 9 doses	Subjects' subjective scoring of runny nose & sneezing 90 min after 2nd & 4th doses	Significantly reduced runny nose & sneezing with doxylamine
	D'Agostino et al. 1998	Meta-analysis of raw data from 8 double-blind placebo-controlled studies, including 6 on doxylamine, to evaluate the effectiveness of antihistamines to reduce the symptoms of runny nose & sneezing over the first 2 days of medication for subjects with common colds that began within 24-48 hr before entry into the study	Doxylamine succinate 7.5 mg 4 times/day	Statistical analysis of data on severity of runny nose & sneezing	Homogeneity of treatment effect across studies & consistency confirmed for pooling the studies; antihistamines shown to be statistically significantly more effective than placebo in reducing severity of runny nose and sneezing

	Thackray 1978	Double-blind crossover controlled trial (n=70) of a combination of doxylamine + ephedrine + dextromethorphan + acetaminophen in subjects (18 – 60 years) with common cold	Doxylamine succinate 7.5 mg + ephedrine sulfate 8 mg + dextromethorphan HBr 15 mg + acetaminophen 600 mg or control syrup in single 30-ml bedtime dose on 2 consecutive nights: one group of 35 (average age 33.2 yr) took active formula 1st night & control syrup on 2nd night, & other group of 35 (average age 34.7 yr) took control syrup 1st night & active formula on 2nd night	Subjects' subjective assessment each morning of relief from symptoms (cough, nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep) & additional-ly on the 2nd morning of which formulation they found to be more effective at relieving global cold symptoms	Significant degree of relief by active formulation compared to control syrup for cough (highly significant difference between groups), nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep; highly significant number of subjects preferred global symptomatic relief from active formulation
	Mizoguchi et al. 2007	Double-blind placebo (n=208)-controlled trial of a combination (n=224) of doxlyamine + dextromethorphan + acetaminophen + ephedrine in subjects (18 – 64 yr, mean 31.3 yr) with common cold symptoms for 1-5 days with at least moderate nasal congestion & a runny nose, at least mild cough, & at least mild pain with one or more of the following: sore throat, sore chest, headache, or body pain/aches	Doxylamine succinate 7.5 mg + dextromethorphan HBr 15 mg + acetaminophen 600 mg + ephedrine sulfate 8 mg in one 30-ml evening dose	Subjects' subjective scoring of symptoms (nasal conges-tion, runny nose, cough, and pain) 3 hr post-dosing and 1 hr after rising the next morning	For primary endpoint (composite of nasal congestion/runny nose/cough/ pain relief scores 3 hr post-dosing), clinically & statistically signifi-cantly greater relief with treatment (p=0.0002); statis-tically significant improve-ment with treatment in each individual symptom score 3 hr post-dosing (p≤0.017); clinically & statistically significant greater benefits on composite score & each of the individual symptoms the next morning in those who had received treatment (p≤0.003)

A 1-5. **Pharmacokinetic and Efficacy Summaries for OTC Phenylephrine**

1. Active Ingredient
   - Name of ingredient: Phenylephrine hydrochloride; phenylephrine bitartrate
   - Pharmacotherapeutic class: Nasal decongestant

2. Indication According to OTC Monograph

   Either of the following: "For the temporary relief of nasal congestion" or "Temporarily relieves nasal congestion," which may be followed by any of the following: "due to" (either) ""the common cold" or "a cold"; "due to" (any one of the following) "hay fever," Hay fever (allergic rhinitis)," "hay fever or other upper respiratory allergies," or "hay fever or other upper respiratory allergies (allergic rhinitis)."

3. Dosage According to OTC Monograph

	< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
For products containing phenylephrine hydrochloride	"Consult a doctor"	2.5 mg every 4 hr, not to exceed 15 mg in 24 hr	5 mg every 4 hr, not to exceed 30 mg in 24 hr	10 mg every 4 hr, not to exceed 60 mg in 24 hr		"Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor." "Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor."
For products containing phenylephrine bitartrate	"Ask a doctor"	"Ask a doctor"	7.8 mg every 4 hr, not to exceed 31.2 mg in 24 hr	15.6 mg every 4 hr, not to exceed 62.4 mg in 24 hr		

4. Pharmacokinetic Characteristics

   No data from pediatric pharmacokinetic studies are available.

5. Efficacy Study Summaries for Phenylephrine

These summaries are from published randomized, placebo-controlled studies of phenylephrine alone or in combination with other drug active ingredients and a meta-analysis of data from randomized, placebo-controlled studies

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Hutton et al. 1991	[see below]			
6 months - <6 years	Hutton et al. 1991	Double-blind placebo (n=27)-controlled trial of fixed combination (n=36) of brompheniramine, phenylephrine, & phenylpropanolamine in children (0.5-5 yr, mean 25 ± 15.7 months) with signs of upper respiratory infection (i.e., nasal congestion or rhinorrhea); also a "no treatment" group (n=33)	Fixed combination of brompheniramine maleate (4 mg/5 ml), phenylephrine HCl (5 mg/5 ml), & phenyl-propanolamine HCl (5 mg/5 ml) given 3 times/ day so that brompheniramine dosage was 0.5-0.75 mg/kg body weight/day, which would mean phenylephrine was at 0.625-0.938 mg/kg/day, for 2 days	Parents' subjective assessment of symptoms (congested or runny nose, breathing trouble, fever, cough, decreased appetite, crankiness, sleep disturbance, & excessive sleepiness) at 48 hr	No differences among groups in individual or composite symptom score changes
6 - <12 years	No studies available				
≥12 years & Adults	Cohen 1972	Double-blind trial with single doses of phenylephrine and placebo in 48 subjects with nasal congestion associated with common cold	Phenylephrine 10, 15, & 25 mg one-time single dose	Objective determination of nasal flow/resistance by electronic posterior rhinometry and subjects' subjective estimation of nasal congestion	Decreased nasal flow/ resistance with all 3 doses of phenylephrine, which was apparent at 15 min, maximal between 30 & 90 min, and still present 120 min after treatment
	Kollar et al. 2007	Meta-analysis of the efficacy of a single dose of phenylephrine for relief of nasal congestion associated with common cold (pooled data from 7 placebo-controlled crossover studies; total n=113)	Phenylephrine 10 mg one-time single dose	Calculated change in objectively measured nasal airway resistance	Meta-analysis supports effectiveness of a single oral dose of phenylephrine

A 1-6. **Pharmacokinetic and Efficacy Summaries for OTC Pseudoephedrine**

1. Active Ingredient
   - Name of ingredient: Pseudoephedrine hydrochloride; pseudoephedrine sulfate
   - Pharmacotherapeutic class: Nasal decongestant

2. Indication According to OTC Monograph
   Either of the following: “For the temporary relief of nasal congestion” or “Temporarily relieves nasal congestion,” which may be followed by any of the following: “due to” (either) “”the common cold” or “a cold”; “due to” (any one of the following) “hay fever,” “hay fever (allergic rhinitis),” “hay fever or other upper respiratory allergies,” or “hay fever or other upper respiratory allergies (allergic rhinitis).”

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
“Consult a doctor”	15 mg every 4-6 hr, not to exceed 60 mg in 24 hr	30 mg every 4-6 hr, not to exceed 120 mg in 24 hr	60 mg every 4-6 hr, not to exceed 240 mg in 24 hr		“Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor.” “Do not give this product to a child who has heart disease, high blood pressure, thyroid disease, or diabetes unless directed by a doctor.”

4. Pharmacokinetic Characteristics

Pseudoephedrine hydrochloride

Publication Reference & Study Characteristics	*Simons et al. 1996;* Single-dose study in 21 children (age 8.8 ± 0.3 yr, weight 32 ± 1 kg); syrup		*Auritt et al. 1981*; Single-dose study in 5 children (age 6 - 12 yr) and 19 adults (age not reported); syrup		Williams et al. 1984.; Single-dose study in 20 healthy male volunteers (age 23.8 ± 5.7 yr, weight 70.4 ± 7.5 kg); syrup
	Children		Children	Adults	Adults
Results:	30 mg dose	60 mg dose	2 mg/kg, 60 mg max.	60 mg dose	60 mg dose
AUC *(ng/mL/hr)*	1260 ± 126	2414 ± 336	*not reported*	*not reported*	1657.7 ± 411.1
t_{max} *(hr)*	2.1 ± 0.3	2.4 ± 0.2	1.86	1.49	1.53 ± 0.91
C_{max} *(ng/mL)*	244 ± 21	492 ± 72	338	211	179.3 ± 24.5
Vd *(L/kg)*	2.6 ± 0.3	2.4 ± 0.4	3.33	2.83	3.4 ± 0.5
t½ *(hr)*	3.1 ± 0.5	3.1 ± 0.4	4.61	5.46	5.46 ±1.29
Cl *(mL/min/kg)*	10.3 ± 1.2	9.2 ± 0.7	8.5	6.27	7.7 ± 2.0

5. Efficacy Study Summaries for Pseudoephedrine

These summaries are from published randomized, placebo-controlled studies of pseudoephedrine alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	No studies available				
2 - <6 years	Gallardo et al. 1994	[see below]			
2 - 16 years	Gallardo et al. 1994	Double-blind placebo-controlled trial of pseudo-ehedrine alone (n=15) and in combination (n=20) with naproxen in subjects 2-16 yr with common colds	Every 8 hr for 5 days: 2 – 5 yr pseudoephedrine 15 mg alone or combined with naproxen sodium 50 mg 6 – 9 yr pseudoephedrine 30 mg alone or combined with naproxen sodium 100 mg 10 – 12 mg pseudoephedrine 45 mg alone or combined with naproxen sodium 150 mg 13 – 16 yr pseudoephedrine 60 mg alone or combined with naproxen sodium 200 mg	Physician evaluation of signs & symptoms (nasal discharge, nasal edema, nasal erythema, conjunctival hyperemia, lacrimation, sneezing, guttural voice, fever, nasal congestion, anosmia odynophagia, head-ache, & malaise) initially & after 3rd 7 5th days	Significantly shorter duration of nasal obstruction, mucosal edema, lacrimation, & headache with combi-nation (pseudoephedrine + naproxen); higher symptom relief after 3rd & 5th day with the combination compared to other groups
≥ 12 years & Adults	Bye at al. 1980	Double-blind placebo (n=60)-controlled comparison of pseudo-ephedrine alone (n=61) & in combination with triprolidine (n=55) in adults with common cold	Pseudoephedrine HCl 60 mg, pseudoephedrine HCl 60 mg + triprolidine HCl 2.5 mg, or placebo 3 times/day for as long as participants thought necessary	Subjects' subjective assessment of 12 specified symptoms using a 4-point scale (cold in the head, running nose, sneezing, blocked nose, sore throat, headache, cough, feeling ill, phlegm, hoarseness, ache in back or limps, feeling feverish); overall treatment response	Sneezing, nasal obstruction and overall responses to treatment significantly improved with pseudo-ephedrine & pseudo-ephedrine + triprolidine compared with placebo ($p < 0.01$); other specific symptoms not significantly affected by treatments

	Sperber et al. 1989	Double-blind placebo (n=10)-controlled comparison of pseudo-ephedrine alone (n=23) & in combination with ibuprofen (n=23) in young adults intranasally inoculated with rhinovirus 30 hr before treatment begun	Pseudoephedrine HCl 60 mg, pseuodephedrine HCl 60 mg + ibuprofen 200 mg, or placebo 4 times/day for 4 ½ days (total of 18 doses)	Objective measurement of oral temperature, nasal secretion weights, and nasal patency (rhinometry); subjects' subjective symptom (nose, throat, systemic) scoring	Total symptom scores reduced by 59% by pseudo-ephedrine + ibuprofen and 48% by pseudoephedrine alone, but only nasal symptom scores were substantially different between the groups; significantly less rhinorrhea (nasal secretion weights) in both pseudoephedrine treatment groups; nasal patency most improved in subjects given pseudo-ephedrine + ibuprofen
	Taverner et al. 1999	Double-blind placebo (n=27)-controlled trial of pseudoephedrine (n=25) in subjects with common cold (<5 days) & moderate-to-severe nasal congestion	Pseudoephedrine 60 mg one-time single dose	Objective measurement of nasal cross-sectional area and volume by acoustic rhinometry at 30 min and then every 30 min up to 180 min; subjects' subjective scoring of congestion symptoms	Total nasal minimum cross-sectional area & nasal volume significantly increased by pseudo-ephedrine, with associated reduction in symptom of congestion
	Eccles et al. 2005	Double-blind placebo (n=119)-controlled trial of pseudoephedrine (n=119) in subjects with moderate nasal congestion associated with common cold (<72 hr)	Pseudoephedrine HCl 60 mg 4 times/day for 3 days	Objective measurement of nasal airway resistance by posterior rhinomanometry and objective scoring (visual analogue scale) of nasal congestion every hour for 4 hr after 1st dose on day 1 and after the last dose on day 3	Significantly decreased nasal airway resistance 2-4 hr after 1st dose of pseudoephedrine on day 1 & 0-4 hr after last dose on day 3; lower subjective congestion scores after one dose of pseudoephedrine on day 1 but not after multiple doses on day 3
	Latte & Taverner 2006	Double-blind placebo-controlled trial (n=216) of pseudoephedrine	Pseudoephedrine HCl 60 mg 4 times/day for 3-4 days	Objective measurement of nasal airway resistance by posterior rhinomanometry and objective scoring (visual analogue scale) of symptom severity	Decreased nasal airway resistance and improved symptoms of congestion in subjects taking pseudoephedrine

	Loose & Winkel 2004	Double-blind placebo (n=162)-controlled trial of a combination of pseudo-ephedrine + acetylsalicylic acid (ASA) [see numbers of subjects under "Treatment"] in subjects with nasal congestion associated with common cold; secondarily com-pared effects of pseudoephedrine-ASA combination with those of a combination of pseudoephedrine + acetaminophen	One-time single doses of pseudoephedrine 60 mg + ASA 1,000 mg [n=161]; pseudoephedrine 30 mg + ASA 500 mg [n= 161]; or pseudoephedrine 60 mg + acetaminophen 1,0000 mg [n=159]	Subjects' subjective assessment of nasal congestion, with primary efficacy variable being area under the curve for differences from baseline on a nasal congestion scale in first 2 hr after treatment	All active treatments statistically significantly superior to placebo; combination of pseudo-ephedrine 60 mg + ASA 1,000 mg shown efficacious for all subjects for entire 6 hr, with significant results for nasal congestion & relief of nasal stuffiness
	Berkowitz et al. 1989	Double-blind placebo (n=141)-controlled trial of a combination of pseudo-ephedrine + loratadine (n= 142) in subjects with common cold	Pseudoephedrine 120 mg + loratadine 5 mg 2 times/day for 5 days	Physician assessment of overall response and evaluation of severity scores for rhinorrhea, nasal patency, & swelling on days 3 & 5; subjects' subjective scoring of overall response and symptoms	Evaluations by both subjects & physicians suggest superiority of the pseudoephedrine-loratadine combination over placebo in relieving symptoms, including nasal congestion, sneezing, postnasal drain-age, and nasal discharge
	Gallardo et al. 1994	[see above]			
	Blanco de la Mora et al. 2000	Double-blind placebo-controlled trial of a combination of pseudo-ephedrine + loratadine + acetaminophen (total n=40)	Pseudoephedrine 60 mg + loratadine 2.5 mg + acetaminophen 500 mg [per tablet or in 2 tablets?], 2 tablets every 12 hr for 5 days	Investigator subjective assessment of nasal congestion, rhinorrhea, & general malaise on days 3 & 5; subjects' subjective evaluation of symptoms	Significant difference between treatment groups on 3rd treatment day; a favorable effect on edema of nasal mucosa & significant reduction of rhinorrhea on 3rd day with drug treatment

	Curley et al. 1988	Double-blind placebo (n=35, 28.1±5.2 yr)-controlled trial of a combination (n=38, 33.7±8.8 yr) of pseudoephedrine + dexbrompheniramine in subjects (>18 yr) with symptoms of common cold (12 -72 hr)	Pseudoephedrine sulfate at 120 mg + dexbromphenir-amine maleate at 6 mg 2 times/day for 7 days	Objective pulmonary function testing (spirometry & flow-volume loops) initially & on 4th, 8th, & 14th day; subjects' subjective daily assessment of severity of 17 symptoms (including cough, nasal obstruction, nasal discharge, postnasal drip, throat-clearing, sneezing, sore throat) for 14 days	Reduced postnasal drip & significantly decreased severity of cough, nasal obstruction, nasal discharge, & throat-clearing during first few days with treatment: significantly lower mean severity ranking of cough on 3rd, 4th, & 5th days ($p \leq 0.05$), of nasal discharge on 2nd ($p \leq 0.05$) & 3rd ($p \leq 0.01$) days, of nasal obstruction on 2nd, 3rd ($p \leq 0.01$), 4th ($p \leq 0.05$), & 5th ($p \leq 0.01$) days, & of throat-clearing on 2nd & 3rd days ($p \leq 0.01$); in pulmonary function testing, cough significantly asso-ciated only with presence of extrathoracic, upper airway obstruction identified by inspiratory flow rates

A 1-7. **Pharmacokinetic and Efficacy Summaries for OTC Dextromethorphan**

1. Active Ingredient
   - Name of ingredient: Dextromethorphan; dextromethorphan hydrobromide
   - Pharmacotherapeutic class: Antitussive (cough suppressant)

2. Indication According to OTC Monograph
   "Temporarily" (any one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough due to" (either of the following: "minor bronchial irritation" or "minor throat and bronchial irritation") (either of the following: "a cold" or "the common cold") "or inhaled irritants." or
   "Temporarily" (any one of the following: "alleviates," "calms," "controls," "decreases," "quiets," "reduces," "relieves," or "suppresses") "cough (any one of the following: "as may occur with," "associated with," or "occurring with") (any one of the following: "a cold," "the common cold," or "inhaled irritants.")

3. Dosage* According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	2.5-5 mg every 4 hr or 7.5 mg every 6-8 hr, not to exceed 30 mg in 24 hr, "or as directed by a doctor."	5-10 mg every 4 hr or 15 mg every 6-8 hr, not to exceed 60 mg in 24 hr, "or as directed by a doctor."	10-20 mg every 4 hr or 30 mg every 6-8 hr, not to exceed 120 mg in 24 hr, "or as directed by a doctor."		"Do not use in a child who is taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric, or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your child's prescription drug contains an MAOI, ask a doctor or pharmacist before giving the product."

*Equivalent to dextromethorphan hydrobromide

4. Pharmacokinetic Characteristics

Dextromethorphan hydrobromide

Publication Reference & Study Characteristics	*Schmitt et al. 1997;* Multiple-dose study in 6 children (age 6 - 35 mo, weight 5.6 -11.7 kg); oral solution by naso-gastric tube		*Woodworth et al. 1987;* Multiple-dose study in 24 male healthy volunteers; immediate-release (IR) and controlled-release (CR) oral solution	
	Children*		Adults**	
Results:	0.5 mg/kg every 6 hours starting 24 hr before surgery, followed by 10 mg/kg at intubation but before surgery and 10 mg/kg immediately after the end of surgery. Thereafter, 8 mg/kg every 6 hr until 48 hr post surgery (7 x 8 mg/kg), followed by stepwise weaning over another 48 h (4 x 4 mg/kg, 2x2 mg/kg, 2x1 mg/kg)		30 mg 4 x daily (IR) or 60 mg 2 x daily (CR) for 2 weeks	
Plasma levels *(ng/mL)*	Dextromethorphan *after 7 x 8 mg/kg at 6 hr intervals*	Free Dextrorphan *after 7 x 8 mg/kg at 6 hr intervals*	Dextromethorphan Cmax at steady state	Free Dextrorphan Cmax at steady state
	550 – 1600 estimated from published plasma concentration figures	75 – 500 estimated from published plasma concentration figures	205.5 ± 134.9 (IR) 198.0 ± 139.0 (CR)	152.6 ± 110.1 (IR) 173.1 ± 152.9 (CR)

* DXM used experimentally to investigate its protective effect towards cerebral injury in children undergoing cardiac surgery with cardiopulmonary bypass.
** 10 subjects were intermediate and 14 were slow DXM metabolizers.

5. Efficacy Study Summaries for Dextromethorphan

These summaries are from published randomized, placebo-controlled studies of dextromethorphan alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Taylor et al. 1993	[see below]			
	Korppi et al. 1991	[see below]			
	Reece et al. 1966	[see below]			
2 - <6 years	Taylor et al. 1993	[see below]			
	Paul et al. 2004	[see below]			
	Korppi et al. 1991	[see below]			

≤12 years	Taylor et al.1993	Double-blind placebo (n=13)-controlled comparison of a guaifenesin & dextromethorphan combination (n=19) & a guaifenesin & codeine combination (n=17) in children (18 mo – 12 yr, mean 4.7 ± 2.3 yr) with night cough less than 14 days in duration	Single dose at bedtime on 3 consecutive nights: 18 mo – 5 yr, in 2.5 ml 50 mg guaifenesin combined with 7.5 mg dextromethorphan or with 5 mg codeine 6 – 12 years, in 5 ml 100 mg guaifenesin combined with 15 mg dextromethorphan or with 10 mg codeine	Subjective ratings in the mornings by parents on the amount of coughing, loss of sleep because of coughing, and any noticed posttussive emesis during the previous night; cough scores and composite symptom scores (total of cough score + loss-of-sleep score + posttussive-emesis score) calculated and mean reductions analyzed	Neither combination (guaifenesin + dextro-methorphan nor guaifenesin + codeine) was superior in treating night cough in children.
	Paul et al. 2004	[see below]			
	Korppi et al. 1991	Placebo (n=26)-controlled trial of dextromethorphan (n=24) & of a combination of dextromethorphan + salbutamol in children (1-10 yr, mean 3.8 yr) with cough associated with acute respiratory infection	Dextromethorphan HBr at 1.5 mg/ml with or without salbutamol at 0.2 mg/ml: 5 ml to children <7 yr & 10 ml to those ≥7 yr, 3 times/day for 3 days	Parents' subjective daily scoring of symptoms (frequency & severity of nocturnal cough, frequency & severity of daytime cough) & their daily assessment of child's general condition & end-of-treatment evaluation of overall benefit of medication	Symptom scores dropped significantly in all 3 groups, but no difference between groups for symptom scores nor in reported general conditions on any of the 3 days; marked relief reported for more than half of the patients (56% with dextromethorphan, 66% with combination, & 73% with placebo)

	Reece et al. 1966	Placebo (n=7)-controlled trial of 2 dextromethorphan-containing multi-ingredient antitussives* in children (2 mo -9 yr) hospitalized with respiratory illness & having the symptom of coughing * Two formulations containing in each 5 ml: 1st formulation (n=7) dextromethorphan HBr 15 mg + phenyl-propanolamine HCl 12.5 mg + pheniramine maleate 6.25 mg + pyrilamine maleate 6.25 mg + ammonium Cl 90 mg 2nd formulation (n=8) dextromethorphan HBr 7.5 mg + phenylpropanolamine HCl 8.75 mg + glyceryl guaiacolate 37.5 mg + alcohol 5%	See formulations in preceding column to the left. Every 8 hr, for a total of 5 doses, including each day's last dose being at bedtime: <2 yr 1st formulation: 1.25 ml 2nd formulation: 2.5 ml [equal content of dextromethorphan at 3.75 mg] 2 – 6 yr 1st formulation: 2.5 ml 2nd formulation: 5.0 ml [equal content of dextromethorphan at 7.5 mg] >7 yr 1st formulation: 5.0 ml 2nd formulation: 10 ml [equal content of dextromethorphan at 15 mg] Placebo given in same volumes as for 2nd formulation	Objective evaluation of 8-hr nighttime cough counts (total & in 2-hr increments) from tape recording through a microphone above subject's bed	Both dextromethorphan-containing formulations were more effective than placebo in suppressing cough, with 47% decrease in total 8-hr cough count with the 1st formulation & 37% decrease with the 2nd vs. 15% decrease with placebo

	Reece et al. 1966	Placebo (n=14)-controlled trial of 2 dextromethorphan-containing multi-ingredient antitussives* in children (2 mo – 12 yr, average 3.6 yr) with cough but without chronic respiratory illness * Two formulations containing in each 5 ml: 1st formulation (n=16) dextromethorphan HBr 15 mg + phenyl-propanolamine HCl 12.5 mg + pheniramine maleate 6.25 mg + pyrilamine maleate 6.25 mg + ammonium Cl 90 mg 2nd formulation (n=13) dextromethorphan HBr 7.5 mg + phenylpropanolamine HCL 8.75 mg + glyceryl guaiacolate 37.5 mg + alcohol 5%	Dosage, treatment frequency, & treatment duration unclear	Mothers' subjective assessment of treatment effect and duration of action in stopping cough or reducing frequency of cough recorded on a standard form	Satisfactory antitussive effect reported for all groups, but dextromethorphan-containing formulations were shown to be statistically significantly more effective than placebo in suppressing cough; cough suppressant effect of 46%-56% vs. 21% with placebo

2 – 16.5 years	Paul et al. 2004; Yoder et al. 2006	Double-blind placebo (n=34)-controlled trial of dextromethorphan (n=33) & of diphenhydramine (n=33) in children (2-16.5 yr, mean 4.50 yr) with nocturnal cough associated with upper respiratory infection (average illness duration = 4.21±1.57 days before treatment)	Dextromethorphan (no salt specified) 7.5 mg to 2- to 5-yr-olds, 15 mg to 6- to 11-yr-olds, & 30 mg to those ≥12 years old	Parents' subjective assessment of frequency, severity, & bothersome nature of nocturnal cough of sleep quality for child & parents; also subjective assessments by subsets (n=12 for dextromethorphan; n=13 for placebo) of children (6.2-16.5 yr, median 7.5 yr)	Improvement for all outcomes for all groups; dextromethorphan not superior to placebo in providing nocturnal symptom relief
	Taylor et al. 1993	[see above]			
≥ 12 years & Adults	Tukiainen et al. 1986	Double-blind placebo (n=34)-controlled comparison of dextromethorphan (n=36) & a dextromethorphan-salbutamol combination (n=38) in out-patients who had an acute respiratory infection with cough	Dextromethorphan 30 mg, dextromethorphan 30 mg + salbutamol 2 mg, or placebo 3 times/day for 4 days	Subjects' subjective scoring of daytime cough frequency & severity and nighttime cough severity & breathlessness; objective measurement of sputum quantity; subjective(?) assessment of ease of expectoration	No statistically significant differences between treatments for symptom scores for daytime cough frequency & severity, sputum quantity or ease of expectoration; combination superior in suppressing nighttime cough, although improvement in all groups during the 4-day treatment period; significant improvement in daytime cough in all groups

	Parvez et al. 1996	Three double-blind placebo-controlled trials (n = 108, 134, & 209) of a single dose of dextromethorphan for acute cough due to acute upper respiratory infection (non-streptococcal); total of 451 subjects	Dextromethorphan 30 mg one-time single dose	Objective quantitative evaluation with a multi-dimensional cough measurement system (microphone & digitized data); subjective patient assessments of cough and rating of troublesomeness of cough	Consistently showed significantly reduced cough counts & total effort, with increased rest periods & unchanged average intensity per cough bout with dextro-methorphan; no treatment effect on subjective assessments with visual analog scale in two studies; in the third study, trend toward improvement in global assessment of cough with dextromethorphan at 120 min & dextromethor-phan shown in ratings of troublesomeness of cough to be significantly superior at 120 min
	Lee et al. 2000	Double-blind placebo (n=22)-controlled trial of a single dose of dextromethorphan (n=21) for subjects (18-46 yr, mean 22.9 yr) with acute cough associated with upper respiratory infection	Dextromethorphan 30 mg one-time single dose	Objective recording of cough frequency (CF) and cough sound pressure level (CSPL); subjective patient assessments of cough severity	Similar trends in dextro-methorphan & placebo groups with statistically significant reductions in CSPL, CF, & subjective scores (but no significant difference between groups); statistically significant greater reduction in mean CSPL from baseline to 90 min with dextromethorphan, but the difference in mean CSPL changes between the 2 groups not significant from baseline to 135 min & to 180 min.

	Pavesi et al. 2001	Meta-analysis of six double-blind placebo (n=354)-controlled clinical trials (may include studies reported by Parvez et al. 1996) of a single dose of dextro-methorphan (n=356) for acute cough due to uncomplicated upper respiratory infections	Dextromethorphan 30 mg one-time single dose	Objective recording continuously for 3 hr after treatment, measuring cough bouts, cough components, cough effort, cough intensity, and cough latency	Meta-analysis showed consistent results across most of the studies for each of the efficacy variables; significantly greater reductions in cough bouts, cough components, and cough effort and an increase in cough latency with dextromethorphan
	Paul et al. 2004; Yoder et al. 2006	[see above]			
	Thackray 1978	Double-blind crossover controlled trial (n=70) of a combination of dextromethorphan + acetaminophen + ephedrine + doxylamine in subjects (18 – 60 yr) with common cold	Dextromethorphan HBr 15 mg + acetaminophen 600 mg + ephedrine sulfate 8 mg + doxylamine succinate 7.5 mg or control syrup in single 30-ml bedtime dose on 2 consecutive nights: one group of 35 (average age 33.2 yr) took active formula 1st night & control syrup on 2nd night, & other group of 35 (average age 34.7 yr) took control syrup 1st night & active formula on 2nd night	Subjects' subjective assessment each morning of relief from symptoms (cough, nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep) & additionally on the 2nd morning of which formulation they found to be more effective at relieving global cold symptoms	Significant degree of relief by active formulation compared to control syrup for cough (highly significant difference between groups), nasal congestion, nasal discharge, sneezing, generally feeling unwell, headache, sore throat, disturbed sleep; highly significant number of subjects preferred global symptomatic relief from active formulation

	Mizoguchi et al. 2007	Double-blind placebo (n=208)-controlled trial of a combination (n=224) of dextromethorphan + doxlyamine + acetaminophen + ephedrine in subjects (18 – 64 yr, mean 31.3 yr) with common cold symptoms for 1-5 days with at least moderate nasal congestion & a runny nose, at least mild cough, & at least mild pain with one or more of the following: sore throat, sore chest, headache, or body pain/aches	Dextromethorphan HBr 15 mg + doxylamine succinate 7.5 mg + acetaminophen 600 mg + ephedrine sulfate 8 mg in one 30-ml evening dose	Subjects' subjective scoring of symptoms (nasal congestion, runny nose, cough, and pain) 3 hr post-dosing and 1 hr after rising the next morning	For primary endpoint (composite of nasal congestion/runny nose/cough/ pain relief scores 3 hr post-dosing), clinically & statistically significantly greater relief with treatment ($p=0.0002$); statistically significant improvement with treatment in each individual symptom score 3 hr post-dosing ($p\leq0.017$); clinically & statistically significant greater benefits on composite score & each of the individual symptoms the next morning in those who had received treatment ($p\leq0.003$)
	Galvez 1985	Double-blind placebo (n=32)-controlled trial of a combination (n=28) of dextromethorphan + pseudoehedrine + azatadine in subjects (12 – 70 yr) with common cold & associated cough, nasal congestion, & rhinorrhea	Dextromethorphan HBr 20 mg + pseudoephedrine sulfate 60 mg + azatadine maleate 1 mg in 5 ml 3 times/day for 5 days	Subjective assessment (4-point scale) by physician (in consultation with subjects) of rhinorrhea, nasal congestion, cough, sneezing, postnasal drip, lacrimation, headache, tiredness/drowsiness, & general achiness the 1st day (before dose) & on 3rd & 5th days	More rapid & complete relief of nasal congestion & cough with treatment; excellent or good thera-peutic responses at interim ($p\leq0.01$) & final ($p<0.01$) evaluations in statistically greater number of subjects with treatment, & faster onset of symptommatic relief (reported at 12 hr by 55% treated subjects vs. 17% with placebo); excellent or good overall responses by 3rd day in 60% of treated vs. 8% of placebo subjects, & by 5th day in 77% of treated vs. 21% with placebo

	Scavino 1985	Double-blind placebo (n=29)-controlled trial of a combination (n=29) of dextro-methorphan + doxlyamine + acetaminophen + ephedrine in subjects (12-66 years) with common cold & associated cough (symptomatic 24-48 hr before enrollment)	Dextromethorphan HBr 20 mg + pseudoephedrine sulfate 60 mg + azatadine maleate 1 mg in 5 ml 3 times/day for 5 days	Subjective assessment (4-point scale) by physician of symptoms (in consultation with subjects: rhinorrhea, nasal congestion, cough, sneezing, postnasal drip, & lacrimation) & signs (swelling & hyperemia of nasopharyngeal mucosa, nasal secretions, & hyperemia) the 1st day (before dose) & on 3rd & 5th days; physician evaluation of overall therapeutic response on 3rd & 5th days	Statistically significantly more reduction in symptom severity scores at interim ($p<0.01$) & final evaluations ($p<0.01$) with treatment (59% improvement vs. 33% with placebo on 3rd day; 92% vs. 69% on 5th day), as well as faster onset of symptomatic relief (reported at 12 hr or less by 40% of treated subjects vs. none with placebo; more rapid improvement (lessened severity) in signs with treatment, & statistically significant difference ($p<0.01$) (57% improvement vs. 30% with placebo on 3rd day; 93% vs. 73% on 5th day); excellent or good overall therapeutic responses by 3rd day in 76% of treated subjects vs. 17% of placebo group, & by 5th day in 88% of treated vs. 48% with placebo

A 1-8. **Pharmacokinetic and Efficacy Summaries for OTC Guaifenesin**

1. Active Ingredient
   - Name of ingredient: Guaifenesin
   - Pharmacotherapeutic class: Expectorant

2. Indication According to OTC Monograph
   "Helps loosen phlegm (mucus) and thin bronchial secretions to" (one or more of the following: "rid the bronchial passageways of bothersome mucus," "drain bronchial tubes," and "make coughs more productive").

3. Dosage According to OTC Monograph

< 2 years	2 – <6 years	6 - <12 years	≥12 years & Adults	Professional Labeling	Special Instructions
"Consult a doctor"	50-100 mg every 4 hr, not to exceed 600 mg in 24 hr [NDA products say "children under 12 years of age: do not use"]	100-200 mg every 4 hr, not to exceed 1,200 mg in 24 hr [NDA products say "children under 12 years of age: do not use"]	200–400 mg every 4 hr, not to exceed 2,400 mg in 24 hr	"Helps loosen phlegm and thin bronchial secretions in patients with stable chronic bronchitis."	For products labeled only for children < 6 yr: "Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

4. Pharmacokinetic Characteristics

   No data from pediatric pharmacokinetic studies are available.

5. Efficacy Study Summaries for Guaifenesin

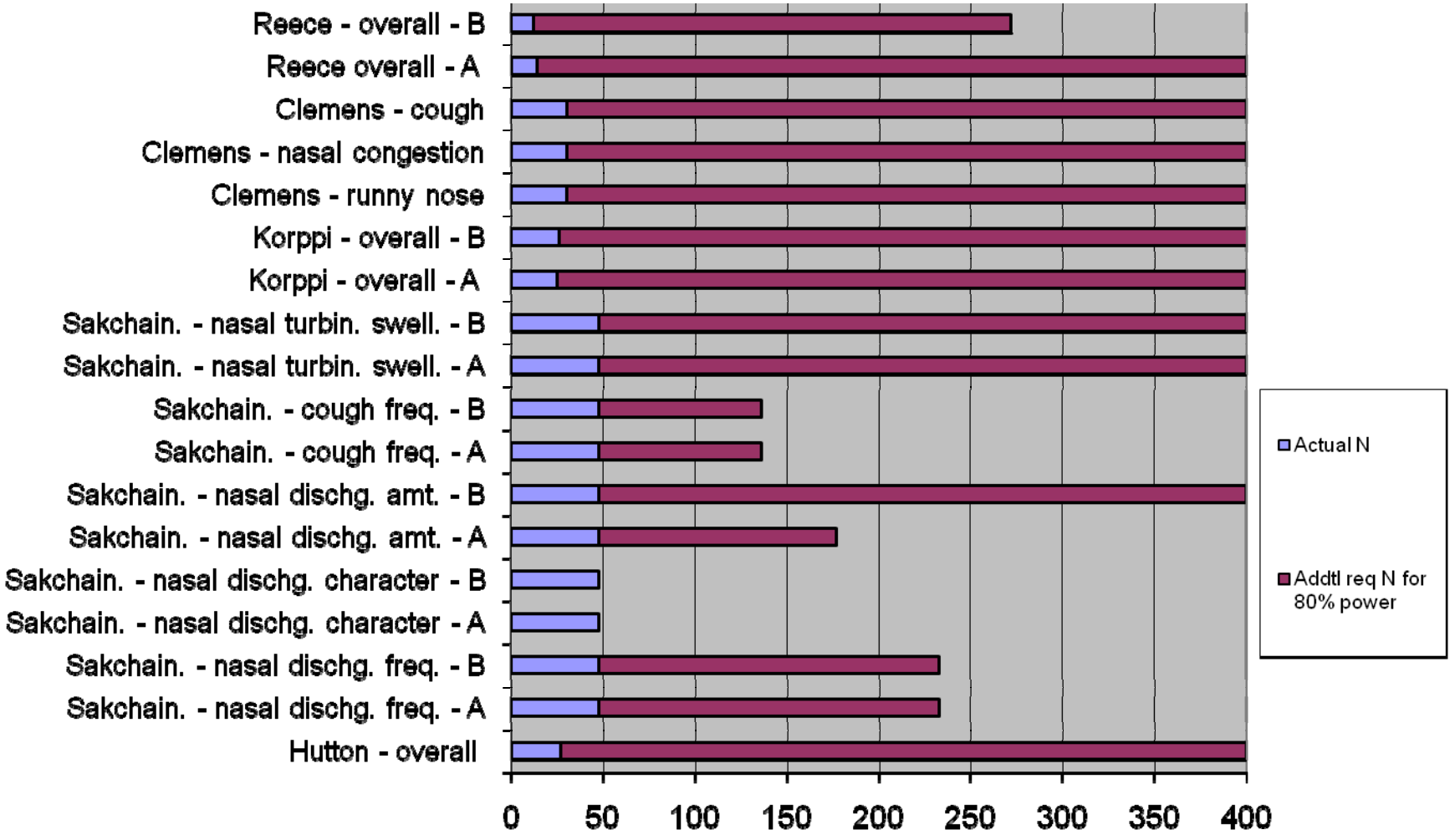
These summaries are from published randomized, placebo-controlled studies of guaifenesin alone or in combination with other drug active ingredients.

Age Group	Study ID	Study Design / Sample Size	Treatment	Method of Measuring Outcomes	Results
< 2 years	Taylor et al. 1993	[See below]			
2 - <6 years	Taylor et al. 1993	[See below]			
18 months - ≤12 years	Taylor et al. 1993	Double-blind placebo (n=13)-controlled comparison of a guaifenesin & dextromethorphan combination (n=19) & a guaifenesin & codeine combination (n=17) in children (18 mo- 12 yr, mean age 4.7±2.3 yr) with night cough less than 14 days in duration	Single dose at bedtime on 3 consecutive nights: 18 mo – 5 yr, in 2.5 ml 50 mg guaifenesin combined with 7.5 mg dextromethorphan or with 5 mg codeine 6 – 12 yr, in 5 ml 100 mg guaifenesin combined with 15 mg dextromethorphan or with 10 mg codeine	Subjective ratings in the mornings by parents on the amount of coughing, loss of sleep because of coughing, and any noticed posttussive emesis during the previous night; cough scores and composite symptom scores (total of cough score + loss-of-sleep score + posttussive-emesis score) calculated and mean reductions analyzed	Neither combination (guaifenesin + dextro-methorphan nor guaifenesin + codeine) superior in treating night cough in children
> 12 years & Adults	Robinson et al. 1977	Double-blind multi-investigator placebo (n=121)-controlled trial of guaifenesin (n=118) in subjects, >18 years, with moderate to severe cough associated with upper respiratory infection	200 mg guaifenesin (in 10 ml) 4 times/day for 3 days	Subjective rating by subjects initially and at 24, 48, and 72 hr; physician evaluation initially & at 72 hr; objective measure of sputum characteristics	Guaifenesin significantly reduced cough frequency, cough intensity, and chest discomfort in subjects with initial nonproductive and productive cough and significantly increased sputum volume and facilitated raising sputum in subjects with initial productive cough.

	Kuhn et al. 1982	Double-blind placebo (n=32)-controlled trial of guaifenesin (n=33) in subjects, 18-30 years, with acute respiratory illness of less than 48 hours' duration with cough	400 mg guaifenesin in 30ml every 6 hr for 30 hr (total of 2,400 mg)	Objective recorded cough counting for 42 subjects during 24-hr baseline & 36-hr treatment periods; subjective rating by subjects on frequency of cough, cough severity, cough discomfort, chest discomfort, sputum quantity, & sputum thickness	Guaifenesin showed no antitussive effect but was associated with a perceived decrease in sputum quantity & a reduction in sputum thickness.
	Parvez et al. 1996	Double-blind placebo (n=29)-controlled trial of guaifenesin (n=31) in adults with chronic cough	1200 mg/day guaifenesin for 14 days	Sputum collected, weighed and volume measured. Sputum concentrations of a sputum glycoprotein marker, fucose, were also measured. Objective recording of cough; Subjective patient assessment of ease of expectoration	GUA-treated patients maintained a steady sputum volume output over the study period with a significant difference to placebo of 37% on day 14. Fucose was significantly reduced in the GUA vs the placebo group on day 14. A subgroup of high sputum producers (>40mL pre-treatment) reported a large and significant improvement in ease of expectoration. GUA also produced larger reductions in average intensity per cough compared to placebo on days 4 and 7 which was statistically significant on day 4 ($p<0.05$).

Appendix 2. *Post hoc* Statistical Analysis of 8 Pediatric Clinical Trials

Sample sizes necessary to achieve statistical significance at 80% power based on effect size observed in pediatric studies



If a study has two comparators, they are distinguished by the letter after the lead author's name.

Data from 8 published pediatric randomized controlled trials, with calculation of the sample size required to achieve statistical significance at 80% based on the power (page 1 of 2)

Article (active/placebo group sample sizes)	**Relevant endpoint**	**Observed difference from placebo (+ values indicative of efficacy) (within-group size reqd for the difference to be significant*)**	**Standard deviation (S) or relevant related data[1]**	**True difference that is detectable with 80% power**	**Clinically meaningful difference cited in article / Power / within-grp size reqd for 80% power**
Hutton et al (30/24)	a) % subjects improved overall b) Relative amt of improvement (averaged across 9 symptoms on standardized scales)	a) -4% b) -0.10	a) Placebo improvement rate: 71% b) S = 0.506[3]	a) 29% b) 0.40	a) NP[2] b) NP
Sakchainanont el al (48/48/47) (2 active groups)	% subjects improved: a) nasal discharge frequency b) nasal discharge character c) nasal discharge amount d) cough frequency e) nasal turbinate swelling	Act. 1 / Act. 2 a) 9% (233) / 13% (113) b) 30% (28) / 30% (28) c) 12% (177) / 7% (421) d) 12% (136) / 12% (136) e) 2% (3396) / -3%	Placebo improvement rate[4] : a) 62% b) 43% c) 47% d) 28% e) 21%	 a) 27% b) 30% c) 30% d) 30% e) 29%	NP
Yoder et al (12/12/13) (2 active groups)	a) Chg from baseline (BL) of a cough frequency assessment on a 0-6 scale b) Sum of chg from BL of four cough assessments, each on a 0-6 scale	a) Active 1: 0.20 (505) Active 2: 0.37 (149) b) Active 1: 4.04 (27) Active 2: 0.13 (25,000)	a) S = 1.62[3] b) S = 7.38[3]	a) 1.90 b) 8.64	a) 1 unit / 32% / 43 b) NP
Taylor et al (19/13) (only DM active group considered)	Chg from BL of a cough assessment on a 0-4 scale	NA	NP[5]	NA	NA
Paul et al (33/33/34) (2 active groups)	a) Chg from BL of a cough frequency assessment on a 0-6 scale b) Sum of chg from BL of five cough assessments, each on a 0-6 scale	a) Active 1: -0.27 Active 2: -0.27 b) Active 1: 0.94 (450) Active 2: -0.79	a) S = 1.18[3] b) S = 7.18[3]	a) 0.82 b) 4.99	a) 1 unit / 93% / 23 b) NP

Data from 8 published pediatric randomized controlled trials, with calculation of the sample size required to achieve statistical significance at 80% based on the power (page 2 of 2)

Korppi et al (25/24/26) (2 active groups)	a) Sum of chg from BL of four cough assessments, each on a 0-3 scale b) General condition on a 0-3 scale c) % subjects improved	a) NA b) NA c) Active 1: -16% Active 2: 5% (503) [based on 22/19/24 subjects]	a) NP b) NP c) Placebo improvement rate: 79% (based on 24 subjects)	a) NA b) NA c) No value exists[6]	NP
Clemens et al (28/31)	a) Relief of various cold symptoms, each assessed on a 0-6 scale b) % subjects improved: i) runny nose ii) nasal congestion iii) cough	a) NA b) i) -8% ii) -2% iii) 8% (563)	a) NP b) Placebo % improvement rates[7]: i) 58 ii) 51 iii) 43	a) NA b) i) 34% ii) 36% iii) 38%	a) NA b) NP
Reece et al (7/8/7 in inpatient study; 16/13/14 in ambulatory study) (2 active groups)	a) Chg from BL in total daily cough count (inpatient study) b) % subjects with satisfactory response (ambulatory study)	a) Active 1: 59.1 (20) Active 2: 72.0 (14) b) Active 1: 7% (481) Active 2: 8% (272) [based on 15/12/12 subjects]	a) S = 92.5[8] b) Placebo % improvement rate: 67 (based on 12 subjects)	a) 150.9/145.1[9] b) No value exists[6]	NP

NP: Not provided (insufficient information)
NA: Not applicable since power calculations cannot be done
*: Computed only when active treatment is numerically superior to placebo

[1] Power calculations depend on the standard deviation under the null hypothesis (active ineffective). With dichotomous data, such as % of subjects improved, this standard deviation is related to the average of the within-group improvement rates, and under the null hypothesis, the active improvement rate is the same as the placebo rate.

[2] Article cited as meaningful that the percent of subjects receiving active treatment be 28% higher than no treatment. But the meaningful difference should be versus placebo since large placebo effects are typically seen in these studies.

[3] Computed from the observed means and overall p-values provided in the article

[4] Percentages of subjects with a worsened or unchanged condition were combined for calculations.

[5] The within-day data were analyzed non-parametrically (Mann-Whitney tests) for which the provided p-values are insufficient for power calculations. Sometimes the non-parametric p-values can be assumed to be close to the parametric ones and thus could be used for the power calculations; unfortunately an examination of the observed means and p-values here suggest that the non-parametric p-values would be poor estimates of the parametric ones.

[6] Even if the active improvement rate is 100%, this study cannot detect a significant difference with 80% power.

[7] These rates assume that within each group the % of subjects improving is the same as the % of reports of improvement, which appear in the article.

[8] Computed from the raw data provided in article

[9] Detectable differences versus placebo for Active 1/Active 2; value slightly smaller for Active 2 due to its slightly larger sample size

Appendix 3. Supportive Tables for Section 4 (Pharmacokinetics)

Appendix 3. Supportive Tables for Section 4 (Pharmacokinetics)

Available Pseudoephedrine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for pseudoephedrine in 119 children ages 2 through 11 years old were collected from a multiple-dose study [McNeil 1999], two published single-dose studies [Auritt 1981, Simons 1996], and three single-dose studies for pediatric cold/allergy/sinus OTC products [Wyeth 2002a, Wyeth 2004]. FDA had summarized data for the latter studies as part of the basis of approval for new drug applications, NDA 21-373 and 21-587, and these summaries are publicly available per the Freedom of Information Act. The dose-independent pharmacokinetic parameters, oral clearance CL/F, half-life t½, and apparent distribution volume Vd/F from studies in children and adults are listed in Table 4.5; whereas, the doses and drug exposure parameters (AUC_{INF} and C_{MAX}) are listed in Table 4.6.

Table 4.5 Dose-Independent Pharmacokinetic Parameters (Mean, cv%) for Pseudoephedrine by Age Group

Age Group (Study Reference)	n	Age (y)	t ½ (h)	CL/F (mL/kg/min)	Vd/F (L/kg)
Adults 18 to 45 years	***147***	***28***	***6.3***	***6.5***	***3.3***
McNeil 1987 (Study 87-744)	24	29 ± 5.1	7.0 (20%)	6.4 (36%)	3.7 (17%)
McNeil 1992 (Study 91-104)	12	27 ± 7.3	6.4 (33%)	5.5 (28%)	2.8 (15%)
McNeil 1993 (Study 91-107)	24	30 ± 8.3	5.8 (19%)	7.5 (36%)	3.7 (19%)
Wyeth 2004 (Study AR-00-02)	26	28	5.5 (19%)	7.0 (NR).	NR
Auritt 1981	19	NR	5.5 (NR)	6.3 (NR).	2.8 (NR).
Williams 1984	18	24 ± 5.7	5.6 (19%)	7.3 (25%)	3.3 (12%)
Yacobi 1980	24	19 to 41	7.9 (21%)	5.2 (26%)	3.5 (32%)
Children 6 to < 12 years	***124***	***8.9***	***4.0***	***10.2***	***3.2***
McNeil 1999 (Study 97-024)	19	9.0 ± 1.8	3.3 (17%)	12.7 (17%)	3.5 (20%)
Wyeth 2002a (Study AQ-99-02)[a]	28	8.6 ± 1.6	3.9 (9%)	10.0 (20%)	3.4 (19%)
Wyeth 2002a (Study AQ-99-02)[a]	28	8.6 ± 1.6	4.9 (11%)	NR	NR
Wyeth 2004 (Study AR-00-03)	30	9.0	4.2 (15%)	9.3 (NR).	NR
Auritt 1981	5	NR	4.6 (NR)	8.5 (NR)	3.3 (NR).
Simons 1996[b]	7	8.8 ± 0.3	3.1 (16%)	10.3 (28%)	2.6 (12%)
Simons 1996[b]	7	8.8 ± 0.3	3.1 (13%)	9.2 (8%)	2.4 (17%)
Children 2 to < 6 years	***23***	***3.9***	***4.8***	***11.4***	***4.0***
McNeil 1999 (Study 97-024)	4	5.0 ± 0.7	3.8 (29%)	11.4 (21%)	3.6 (9%)
Wyeth 2002a (Study AQ-00-04)[c]	9	3.8 ± 1.2	4.7 (34%)	11.4 (34%)	4.2 (21%)
Wyeth 2002a (Study AQ-00-04)[c]	10	3.6 ± 1.3	5.3 (36%)	NR	NR

a: crossover study with 28 children; b: parallel-group study with 7 and 7 children, ages reported for all enrolled subjects; c: parallel-group study with 9 and 10 children; NR = not reported.

Table 4.6 Dose-Dependent Pharmacokinetic Parameters[a] (Mean, cv%) for Pseudoephedrine by Age Group

Age Group (Study Reference)	n	Age (y)	Form - C or S	Dose (mg)	AUC_{INF} (ng·h/mL)	AUCtau (ng·h/mL)	C_{MAX} (ng/mL)	T_{MAX} (h)
Adults 18 to 45 years	***139***	***27***	***---***	***60***	***1993***	***---***	***215***	***1.74***
McNeil 1992 (Study 91-104)	12	27 ± 7.3	Tablet-S	60	2594 (28%)	NA	232 (30%)	1.96 (32%)
Wyeth 2002b (Study AD-99-01)	28	26	Tablet-S	60	1801 (25%)	NA	231 (25%)	1.71 (42%)
Wyeth 2002b (Study AD-99-03)	12	30	Tablet-C	60	2066 (22%)	NA	224 (22%)	1.52 (39%)
Wyeth 2004 (Study AR-00-02)	26	28	Liquid-C	60	2085 (20%)	NA	211 (17%)	1.80 (33%)
Auritt 1981	19	NR	Liquid-S	60	NR	NA	211 (NR)	1.49 (NR)
Williams 1984	18	24 ± 5.7	Tablet-S	60	1712 (21%)	NA	180 (17%)	1.94 (44%)
Yacobi 1980	24	19 to 41	Tablet-C	30 x 60	NA	2323 (24%)	NA	NA
Children 6 to < 12 years	***112***	***8.9***	***---***	***31***	***1715***	***---***	***212***	***1.85***
McNeil 1999 (Study 97-024)	19	9.0 ± 1.8	Liquid-C	5 x 35 [b]	NA	1248 (21%)	214 (19%)	1.81 (28%)
Wyeth 2002a (Study AQ-99-02)[c]	28	8.6 ± 1.6	Liquid-C	30	1735 (27%)	NA	218 (24%)	1.87 (43%)
Wyeth 2002a (Study AQ-99-02)[c]	28	8.6 ± 1.6	Liquid-S	30	1767 (32%)	NA	215 (23%)	1.80 (42%)
Wyeth 2004 (Study AR-00-03)	30	9.0	Liquid-C	30	1755 (29%)	NA	195 (24%)	1.85 (35%)
Simons 1996	7	8.8 ± 0.3	Liquid-S	30	1260 (25%)	NA	244 (21%)	2.1 (33%)
Children 2 to < 6 years	***23***	***3.9***	***---***	***16***	***1325***	***---***	***183***	***1.32***
McNeil 1999 (Study 97-024)	4	5.0 ± 0.7	Liquid-C	5 x 20 [b]	NA	1302 (27%)	230 (10%)	1.22 (34%)
Wyeth 2002a (Study AQ-00-04)[d]	9	3.8 ± 1.2	Liquid-C	15	1292 (41%)	NA	179 (17%)	1.21 (69%)
Wyeth 2002a (Study AQ-00-04)[d]	10	3.6 ± 1.3	Liquid-S	15	1355 (41%)	NA	167 (27%)	1.46 (47%)

a: Except T_{MAX}, which is not a dose-dependent parameter, but which is usually reported with C_{MAX}.

b: Dosing regimen for the multiple-dose study of pseudoephedrine 1.125 mg/kg administered every six hours for five doses. The average milligram dose is listed. Both C_{MAX} and T_{MAX} are modeled estimates for the first single dose, whereas AUCtau is the area under curve for the dosing interval (tau) at steady state, which is equivalent to AUC_{INF}.

c: crossover study with 28 children

d: parallel-group study with 9 and 10 children

Key: NA – not applicable; NR – not reported; C – combination pseudoephedrine product; S – single ingredient pseudoephedrine.

Available Chlorpheniramine Pharmacokinetic Data in Children and Adults

Pharmacokinetic data for chlorpheniramine in 41 children ages 6 through 11 years old were collected from a published study [Simons 1982] and a study submitted to FDA to support approval of a pediatric triple ingredient OTC product [Wyeth 2004]. FDA had summarized data for the latter study as part of the basis of approval, and this summary is publicly available. The dose-independent pharmacokinetic parameters, oral clearance CL/F, half-life t½, and apparent distribution volume Vd/F from studies in children and adults are listed in Table 4.7; whereas, the doses and drug exposure parameters (AUC_{INF} and C_{MAX}) are listed in Table 4.8.

Table 4.7 Dose-Independent Pharmacokinetic Parameters (Mean, cv%) for Chlorpheniramine by Age Group

Age Group (Study Reference)	n	Age (y)	t ½ (h)	CL/F (mL/kg/min)	Vd/F (L/kg)
Adults 18 to 45 years	***167***	***----***	***20.2***	***5.0***	***7.65***
Chen 2004	18	NR	18.9 (29%)	NR	NR
Najjar 1995	13	25-45	25.5 (77%)	NR	NR
Huang 1982	5	27 to 40	31.1 (27%)	NR	NR
Koch 1998	24	18 to 40	18.5 (NR)	NR	NR
Kotzan 1982[a]	15	18 to 27	17.3 (25%)	NR	NR
Kotzan 1982[a]	15	18 to 27	14.6 (23%)	NR	NR
Vallner 1982	15	24	25.1 (33%)	NR	NR
van Toor 2001	24	20-41	17.6 (28%)	NR	NR
Wyeth 2004 (Study AR-00-02)	29	28	21.6 (30%)	5.5 (NR)	NR
Yacobi 1980	24	19 to 41	21.0 (24%)	4.40 (32%)	7.65 (27%)
Children 6 to < 12 years	***41***	***9.5***	***13.8***	***8.28***	***7.0***
Simons 1982	11	11.0 ± 3	13.1 (50%)	7.23 (44%)	7.0 (40%)
Wyeth 2004 (Study AR-00-03)	30	9.0	14.0 (28%)	8.67 (NR).	NR

a: crossover study; NR = not reported

Table 4.8 Dose-Dependent Pharmacokinetic Parameters[a] (Mean, cv%) for Chlorpheniramine by Age Group

Age Group (Study Reference)	n	Age (y)	Form - C or S	Dose (mg)	AUC_{INF} (ng·h/mL)	AUCtau	C_{MAX} (ng/mL)	T_{MAX} (h)
Adults 18 to 45 years	***126***	***----***	***----***	***4***	***166.4***	***NA***	***7.37***	***3.3***
Chen 2004	18	NR	Tablet-C	4	164 (43%)	NA	7.25 (32%)	3.5 (51%)
Koch 1998	24	18 to 40	Tablet-S	4	185 (35%)	NA	7.5 (20%)	3.3 (24%)
Kotzan 1982	15	18 to 27	Liquid-S	4	65.4 (33%)	NA	5.9 (39%)	3.4 (73%)
Wyeth 2004 (Study AR-00-02)	29	28	Liquid-C	4	193.5 (39%)	NA	7.95 (16%)	3.2 (43%)
Wyeth 2002b (Study AD-99-01)	28	26	Tablet-S	4	162.5 (44%)	NA	7.27 (27%)	3.4 (45%)
Wyeth 2002b (Study AD-99-03)	12	30	Tablet-C	4	202.6 (51%)	NA	8.00 (41%)	2.9 (30%)
Children 6 to < 12 years								
Wyeth 2004 (Study AR-00-03)	30	9	Liquid-C	2	130.9 (40%)	NA	7.34 (60%)	2.9 (53%)
Adults 18 to 45 years	***96***	***----***	***----***	***8***	***248.1***	***324.6***	***13.5***	***3.0***
Huang 1982	5	27 to 40	Tablet-S	8	NR	NA	18.8 (51%)	2.7 (22%)
Kotzan 1982	15	18 to 27	Liquid-S	8	156.3 (39%)	NA	11.3 (26%)	3.8 (71%)
Najjar 1995	13	25 to 45	Tablet-S	8	431.2[b] (NR)	NA	20.5[b] (NR)	2.1 (52%)
van Toor 2001	24	20 to 41	Tablet-S	8	206.2 (32%)	NA	9.87 (21%)	NR
Vallner 1982	15	24	Tablet-S	28 x 4	NA	311.3[c] (47%)	NA	NA
Yacobi 1980	24	19 to 41	Tablet-C	28 x 4	NA	333.0[c] (44%)	NA	NA
Children 6 to < 12 years								
Simons 1982	11	11.0 ± 3	Liquid-S	4.75[d]	246.2 (51%)	NA	13.5 (26%)	2.5 (60%)

a: Except T_{MAX}, which is not a dose-dependent parameter, but which is usually reported with C_{MAX}.
b: geometric mean
c: AUCtau over 12 hours during which two 4-mg doses were given six hours apart, totaling an 8 mg dose over 12 hours.
d: Dose estimated from mean weight of 39.6 kg and weight-adjusted dose of 0.12 mg/kg.

Key: NA – not applicable; NR – not reported; C – combination pseudoephedrine product; S – single ingredient pseudoephedrine

Appendix 4. Safety Data from Prospective Clinical Trials in Children

APPENDIX 4

Table 5.1 Relevant AAPCC Coding Terminology: Reason for Exposure

Unintentional general	All unintentional exposures not otherwise defined. (*Most exposures of these by curious young children who gain accidental and unsupervised access are coded here)*
Therapeutic error	An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only exposures to medications or products used as medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are know to interact are also included.
Unintentional misuse	Unintentional improper or incorrect use of a nonpharmaceutical substance. Unintentional misuse differs from intentional misuse in that the exposure was unplanned or not forseen by the patient.
Unintentional unknown	An exposure determined to be unintentional, but the exact reason is unknown.
Intentional misuse	An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic or euphoric effect.
Malicious	This category is used to capture patients who are victims of another person's intent to harm them
Adverse reaction	An adverse event occurring with normal, prescribed, labeled, or recommended use of the product, as opposed to overdose, misuse, or abuse. Included are cases with an unwanted effect because of an allergic, hypersensitive, or idiosyncratic response to the active ingredients, inactive ingredients, or excipients. Concomitant use of a contraindicated medication or food is excluded and is coded instead as therapeutic error.

Appendix 4

Table 5.2 Relevant AAPCC Coding Terminology: Medical Outcome Categories

No Effect	The patient did not develop any signs or symptoms as a result of the exposure
Minor Effect	The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucous membranes (e.g., self-limited gastrointestinal symptoms, drowsiness, skin irritation, first-degree dermal burn, sinus tachycardia without hypotension, and transient cough).
Moderate Effect	The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual diability or disfigurement (e.g., corneal abrasion, acid-base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment.
Major Effect:	The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac, or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation).
Death:	The patient died as a result of the exposure or as a direct complication of the exposure. Only those deaths that were probably or undoubtedly related to the exposure are coded here.
Not Followed, Judged as Nontoxic Exposure:	No follow-up calls were made to determine the outcome of the exposure because the substance implicated was nontoxic, the amount implicated was insignificant, or the route of exposure was unlikely to result in a clinical effect.
Not Followed, Minimal Clinical Effects Possible:	No follow-up calls were made to determine the patient's outcome because the exposure was likely to result in only minimal toxicity of a trivial nature (the patient was expected to experience no more than a minor effect).
Unable to follow, judged as a potentially toxic exposure:	The patient was lost to follow-up, refused follow-up, or was not followed, but the exposure was significant and may have resulted in a moderate, major or fatal outcome.
Unrelated effect:	The exposure was probably not responsible for the effect.
Confirmed Nonexposure:	This outcome option was coded to designate cases where there was a reliable and objective evidence that an exposure initially believed to have occurred actually never occurred (e.g., all missing pills are later located).

APPENDIX 4

TABLE 5.3: Maryland Poison Center (MPC) - Medical Outcomes for Calls Involving Cough and Cold Products in Children < 6 years of Age (2004)

AAPCC Medical Outcome Categories	MPC Medical Outcomes N=1078
Confirmed Non-exposure	2 (0.2%)
Unrelated Effect	9 (0.8%)
No Effect	142 (13.2%)
Not Followed, Judged as Nontoxic Exposure	161 (14.9%)
Not Followed, Minimal Effects Possible	682 (63.3%)
Minor Effect	66 (6.1%)
Moderate Effect	5 (0.5%)
Major Effect	0 (0%)
Unable to Follow, Judged as Potentially Toxic Exposure	11 (1%)
Death	0 (0%)

Appendix 4

TABLE 5.5: List of Ingredients* Searched by AAPCC's in National Poisoning and Exposure Database

Brompheniramine	Camphor	Chlophedianol
Chlorcyclizine	**Chlorpheniramine**	Codeine
Dexbrompheniramine	Dexchlorpheniramine	**Dextromethorphan**
Diphenhydramine	**Doxylamine**	Ephedrine
Guaifenesin	Loratidine	Menthol
Naphazoline	Oxymetazoline	Phenindamine
Pheniramine	**Phenylephrine**	Propylhexedrine
Pseudoephedrine	Pyrilamine	Thonzylamine
Triprolidine	Xylometazoline	

***Bold cough and cold ingredients are included in the most frequently purchased pediatric cough and cold products.

Appendix 5. Safety Data from Prospective Clinical Trials in Children

Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
Phase IV Safety and Efficacy Study of C-30 Liquid cough-cold Formula (1980) T&A10 (McNeil)	Open-label and multiple-dose design	30mL = APAP 650 mg, PSE 60 mg, CPM 4 mg, DEX 20 mg Children 6 to < 12 yr 15 mL q 4 hr Adults ≥ 12 yrs 30 mL q 4 hrs	**Population:** 109 subjects with symptoms of upper respiratory infection or allergic rhinitis accompanied by cough completed the study; 73 were adults (over 12 hr) and 36 children (over 6 but under 12 yr). (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 36 (6 <12 yr)). **Safety Results:** 21 AEs were reported in 17/36 children. 15 of the AEs were drowsiness, and 4 of those were reported as severe intensity. 44 AEs were reported in 35/73 adults. 26 of the AEs were drowsiness, and 5 of those were reported as severe intensity. In adults, there were single reports of severe intensity for dizziness, high blood sugar, nausea and high blood pressure. **Conclusions:** A rather high percentage of subjects reported AEs with drowsiness accounting for the majority of reported AEs.
Evaluation of the Efficacy and Safety of C-9-7 Cold Formula in Pediatric Patients with Symptomatology of Upper Respiratory Infection or Allergic Rhinitis (1981) T&A 13 (McNeil)	Open-label and multiple-dose design	10 mL= APAP 320 mg, PSE 30 mg, CPM 2 mg, alcohol 8.5% 10mL q 6-8 hr Up to 4 days	**Population:** 118 children with symptoms of upper respiratory infection or allergic rhinitis between 6 and 12 yrs were enrolled; 117 completed the study. (0 (0< 6 mo), 0 (6 mo<2yr), 0 (2<6 yr), and 117 (6 <12 yr)). **Safety Results:** There were no reports of deaths or serious AEs. 16/117 subjects reported AEs, of which 13/16 were tiredness. 2AEs of tiredness and 1 AE of deep sleep were rated as severe intensity **Conclusions:** 16/117 children reported AEs.
An Evaluation of the Efficacy and Safety of C-30-13 Cough-Cold	Open-label and multiple-dose design	30mL=APAP 650 mg, PSE 60 mg, CPM 4	**Population:** 100 subjects with symptoms of upper respiratory infection or allergic rhinitis accompanied by

Key

APAP=acetaminophen **BRM**=brompheniramine **CLEM**=clemastine **CPM**=chlorpheniramine **DEX**=dextromethorphan
DPH=diphenhydramine **EPH**=ephedrine **GUA**= Guaifensin **IBU**=ibuprofen **LOR=Loratadine**
PE= phenylephrine **PSE**=pseudoephedrine **PPA** =phenylpropanolamine **PBO**=placebo
DB=double-blind **NAR**=nasal airway resistance **OL**=open label

Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
Formula in Adult and Pediatric Patients with Symptomatology of Upper Respiratory Infection or Allergic Rhinitis (1981) T&A 15 (McNeil)		mg, DEX 30 mg, alcohol 7% Children 6 to < 12 yr 15 mL q 6 hr Adults ≥ 12 yrs 30 mL q 6 hrs Up to 4 days	cough completed the study; 50 were adults (over 12 hr) and 50 children (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 50 (6 <12 yr)). **Safety Results:** There were no reported of deaths or serious AEs. 28 AEs were reported in 24 subjects; the majority (10) reported tiredness. AEs reported were of mild or moderate intensity. **Conclusions:** The treatment was tolerated, no safety issues identified.
NDA 21-128 Multiple-dose Pharmacokinetic Study of an Ibuprofen-pseudoephedrine HCl Suspension in Children (1999) (97-024) (McNeil)	Phase I Open-label and multiple-dose design	Dose based on body weight (7.5 mg/kg IBU, 1.125 mg/kg PSE) Dosed q6h for 5 doses	**Population**: 24 healthy children enrolled (24 completed); age 4-11 yrs. (0 (0< 6mo), 0 (6mo<2yr), 4 (2<6 yr), and 20 (6 <12 yr)). **Safety Results:** There were no deaths or serious AEs reported. Overall, 25% of the subjects reported an AE. Drug related AEs reported in 3 (12.5%) of the subjects. All 3 reports were of a stomach ache. None of the subjects withdrew due to AEs **Conclusions:** The treatment was tolerated, no safety issues identified.
NDA 21-128 An Open-Label Study of the Safety of an Ibuprofen-Pseudoephedrine HCl Suspension in Children (1999) (99-086) (McNeil)	Phase III Multi-center, open-label study	Dose based on body weight (12.5 mg/kg IBU, 15 or 30 mg PSE) Dosing: every 6-8 hrs as needed; up to 4 times in 24 hrs for 3 days	**Population:** 114 children enrolled (112 completed); age 2-11 yrs with symptoms of the common cold, flu, or sinusitis. (0 (0<6mo), 0 (6mo<2yr), 66 (2<6yr), 48 (6<12yr)). **Safety Results:** There were no deaths or serious AEs reported. Overall, 18.4% of the subjects reported an AE. Drug related AEs reported in 13.2% of the subjects

Key

APAP=acetaminophen **BRM**=brompheniramine **CLEM**=clemastine **CPM**=chlorpheniramine **DEX**=dextromethorphan
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Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 1. Company Sponsored Studies in Children			
Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
			Most frequently reported AE was somnolence. 2 patients withdrew due to AEs (urticaria, stomach discomfort). **Conclusions:** The treatment was tolerated, no safety issues identified.
NDA 21-373 A Single-Dose, Randomized, Open Label, Three-Way Crossover Pharmacokinetic Study of Children's Advil Cold in 6 to <12 year Old Children AQ-99-02 (Wyeth)	Single dose, RCT, crossover PK study	IBU 100 mg +PSE 15 mg, IBU 100 mg, PSE 15 mg	**Population:** 29 healthy children (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 29 (6 <12 yr)). **Safety Results:** There was only one adverse event in the study of a subject that occurred the night before receiving PSE and therefore was unrelated to treatment. No subject discontinued due to an adverse event. No serious AEs or deaths occurred during the study. No abnormal vital signs were noted. The physical examination and laboratory evaluations results at the end of the study did not reveal any clinically significant findings. **Conclusions:** Treatments were well tolerated. There we no deaths or serious AEs reported.
NDA 21-373 Children's Advil Cold Multiple Dose Safety Study in Children 2 to < 12 Years Old AQ-99-03 (Wyeth)	Open label, uncontrolled safety study	IBU 100 mg/PSE 15 mg/5mL q 6 hrs for up to 7 days (3 days for fever)	**Population:** 106 children with symptomatic rhinitis or sinusitis (2-<12 yr). (0 (0< 6mo), 0 (6mo<2yr), 51 (2<6 yr), and 53 (6 <12 yr)). **Safety Results**: There were no deaths or serious AEs and one patient discontinued due to an AE. A total of 38 AEs were reported by 29 subjects (28%). AEs were most frequently associated with the nervous system (n=11). The most frequently reported AE was somnolence (n=7) followed by vomiting (n=3). Each of

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			the following symptoms had an incidence of two: asthenia, fever, abdominal pain, nausea, tremor, and otitis media. The remaining AEs were single occurrences: back pain, common cold, headache, pain, diarrhea, dyspepsia, lymphadenopathy, lymphocytosis, hyperkinesias, nervousness, rhinitis, pruitus, rash, conjunctivitis, ear disorder, and ear pain. Of the 38 occurrences of AEs. 20 were mild, 16 were rated as moderate and two were rated as severe. The severe AEs were single occurrences of somnolence and ear pain. There were no clinically significant changes in vital signs. **Conclusions:** There were no unexpected or serious adverse events reported during the study.
NDA 21-373 A Single-Dose, Randomized, Open Label, Multicenter, Parallel Group Confirmatory Pharmacokinetic Study of Children's Advil Cold in 2 to < 6 Year Old Children AQ-00-04 (Wyeth)	Single dose, parallel, PK study	IBU 100 mg +PSE 15 mg, PSE 15 mg	**Population:** 23 children < 6 yr with acute respiratory infection. (0 (0< 6mo), 0 (6mo<2yr), 23 (2<6 yr), and 0 (6 <12 yr)). Safety Results: No serious AEs or deaths occurred during the study. No subject discontinued due to an adverse event. Three (27.3%) subjects reported three AEs (one instance each of chills, rhinitis, and otitis media) in the IBU/PSE group, while six (50%) subjects reported severe AEs (one instance each of asthenia, pain, abdominal pain, increased appetite, and rash and two instances of hypertension) in the PSE alone group. Eight of the AEs were rated as mild in severity and the remaining two (otitis media and abdominal pain) were rated as moderate. Except for rhinitis and asthenia, all the AEs were considered not to be related to study

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Citation	**Study Design**	**Dose/Duration**	**Study Populations, Safety Results, Conclusions**
			medication.
NDA 21-587 Children's Allergy Sinus Suspension Single-dose, three period, crossover study in Children 6 to < 12 years AR-00-03 (Wyeth)	Single dose, PK study	IBU 200 mg + PSE 30 mg + CPM 2 mg	**Population:** 32 children with allergic rhinitis. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6yr), and 32 (6 <12yr)). **Safety Results:** No deaths or serious AEs were reported in the study, and no subject discontinued treatment due to an AE**.** Nine (28.1%) subjects reported a total of 10 AEs. Somnolence and pain each occurred in 2 (6.3%) subjects. The incidence of all other AEs reported was limited to 1 subject each. **Conclusions:** There were no unexpected or serious adverse events reported during the study.
NDA 21-587 Children's Allergy Sinus Suspension Multiple-Dose Safety Study in Children 6 to < 12 Years of Age with Symptoms Consistent with Allergic Rhinitis AR-00-04 (Wyeth)	Multicenter, open label, multiple dose safety study	IBU 200 mg + PSE 30 mg + CPM 2 mg q 6 hr for 7 days	**Population:** 111 children 6 to < 12 yr suffering from upper respiratory allergies. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 111 (6 <12 yr)). **Safety Results:** There were a total of 66 AEs reported by 39 (35%) subjects. The most common adverse event in children was somnolence, 13 (12%), which in most cases resolved within two days after study drug was taken. Only two subjects reported experiencing somnolence for longer than two days after receiving the first dose of study medication. Other frequently occurring AEs included asthenia (n=9, 8%), headache (n=6, 5%), and abdominal pain, 5, 5%). Three severe AEs were judged by the investigator to be definitely, probably or possibly related to study drug: somnolence (n=1), and asthenia (n=2). **Conclusions:** AEs noted during the study were

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			consistent with previously known safety profile of same combination drug in adults.
A Comparative Study of Co-administered Doses of Ibuprofen and Pseudoephedrine and Each Drug Alone in the Treatment of Primary Nocturnal Enuresis (2002) (00-131) (McNeil)	Phase II (Therapeutic Exploratory) Double blind, double dummy, placebo controlled, randomized, parallel-group, multiple-center study	(IBU/PSE, IBU/placebo, pseudo/placebo, placebo/placebo) Dose based on body weight (12.5 mg/kg IBU, 15 or 30 mg PSE) Dosed orally at bedtime for 2 weeks	**Population:** 318 children enrolled (307 completed); age 6-11 yrs. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 158 (6 <12 yr) received PSE or PSE + IBU) **Safety Results:** there were no deaths or serious AEs reported. Overall, 21.1% of the subjects reported an AE, no significant difference among treatment groups. Drug related AEs were more frequently reported with IBU/PSE (6.1%) or IBU alone (9.0%) than PSE or placebo. The most frequently reported AEs were headache, infection, abdominal pain, fever, cough increased, taste perversion. 5 subjects withdrew due to digestive system complaints. **Conclusions:** All treatments were tolerated, no safety issues identified.

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Table 2. Literature Review of Safety Data in Children

Citation	Study Design	Dose/Duration	Study Populations, Results, Conclusions
McGovern JP (1959) *Annals of Allergy* 17:915-922	Open label, non-PBO-controlled study	BRM 0.2 mg/kg/d (0<6yr) or 0.15 mg/kg/d (>6 yr) chronic dosing (3 months up to 18 months)	**Population:** 200 children with perennial allergic rhinitis. (1 (0< 6mo), 72 (6mo<2yr), 70 (2<6 yr), and 57 (6 <12 yr)). **Safety Results:** No deaths and no SAEs were reported. Only seven subjects (3.5%) reported AEs; all of them were drowsiness and of mild intensity except in one subject in the 6-12 yr age group that required discontinuation of study medication due to excessive drowsiness. No abnormal hemoglobin, WBC or differential WBC findings were observed **Conclusions:** BRM was safe and well tolerated in infants and children.
Lipschutz A (1960). *Annals of Allergy* 18:998-1003	DB, PBO-controlled trial	PSE QID x 3 days (no dosage given) alone, or PSE + Triprolidine, or PBO.	**Population:** 200 children (156 received PSE or PSE+triprolidine; estimate 100 (0<12yr) **(4 months – 17 years old*)** **Safety Results:** All subjects were administered medication without any ill effects, and no abnormal urinary or hematological findings were observed. **Conclusions:** There were no untoward effects of PSE and PSE with triprolidine in the use of these drugs
Carter, C.H. (1963) The American Journal of the Medical Sciences, 245:713-717.	DB study	A pulvule contained Novrad 50mg (l-PRX) and ASA 325mg was prepared in order to compare to DEX 30mg/ASA 325mg and to ASA 325mg	**Population:** 78 children 1-15 yrs (mean 4.1 yr) with acute UR infections (26 received DEX 0 (0< 6mo), 1 (6mo<2yr), 23 (2<6 yr), and 2 (6 <12 yr). **Safety Results:** No adverse reactions were reported by subjects for any medication. **Conclusions:** The treatments were tolerated, no safety issues identified.

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Reece, C.A. et al. American Journal of Diseases of Children, 112:124—128, 1966.	Twofold study (inpatients hospitalized for respiratory illness and a study of ambulatory patients in private practice)	Triaminicol syrup (each 5ml contains PPA 12.5mg, pheniramine maleate 6.25mg, pyrilamine maleate 6.25mg, DEX 15mg, and ammonium chloride 90mg): Dorcol pediatric cough syrup (each 5ml contains DEX7.5mg, PPA 8.75mg, GUA 37.5, and alcohol, 5%); PBO syrup	**Population**: 65 Children with the chief complaint of cough(22 children 2 mo to 9 yrs in inpatient study and 43 children 2 mo to 12 yrs in the outpatient study).* Two-thirds received DEX containing medication. **Safety Results:** No deaths or SAEs reported. **Conclusions:** No deaths or SAEs reported.
Todd G, et al. *Curr. Med. Res. Opin*. 1975;3:126-131	Two clinical trials: **Trial 1**: DB, randomized, parallel group study. **Trial 2**: DB, randomized, parallel group study.	**Trial 1**: CLEM 1 mg/b.d. increasing to 1 mg t.d.s or q.d.s. if required or CPM 4mg/b.d. increasing to 4 mg t.d.s or q.d.s. if required over the 3-week study period. **Trial 2**: CLEM elixir (0.5 mg/5ml) 1 tsp b.d. increasing by 1-2 tsp as required per physician advice or	**Population: Trial 1**: DB, 58 patients (**9.5-58** years) (28 received CPM)* **Trial 2**: 42 patients completed (**2.5-12.3 years**). (23 received CPM)* **Safety Results:** Summary of Trial 1: Side effects were minimal with both groups and drowsiness was transient with no significant difference in severity or incidence between the groups. Summary Trial 2: The CLEM group had no reports of drowsiness or tiredness; however, there was 1 incidence each of unpleasant taste, facial rash and malaise. The CPM group had 3 complaints of drowsiness and 1 patient had nausea. **Conclusions:** Side effects were minimal and drowsiness was not a problem.

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		CPM syrup (2mg/5 ml) 1 tsp b.d. increasing by 1-2 tsp as required per physician advice over a 3 week study period.	
Simons EFR, et al. *J Allergy Clin Immunol*. 1982;69(4): 376-381	Determine pharmacokinetic parameters of a single dose of CPM	single dose (0.12 mg/kg) of CPM	**Population:** 11 children (**6-16 years**) with allergic rhinitis. (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 6 (6 <12 yr)). **Safety Results:** 10 children had 1 or more mild complaints of sleepiness, dry mouth, excitement, or nausea at 1 and/or 3 hours after CPM administration. The mean score of adverse effects did not differ significantly at 1, 3, 6, 9 and 30 hr from the prestudy score. **Conclusions:** The children experienced only mild transient side effects from CPM over a serum concentration range of 5.5 to 18.5 ng/mL.
Jaffe G, Grimshaw JJ (1983) Cur Med Res Opin 8(8):594-599.	Randomized, Single blind study	Actifed (triprolidine 1.25 mg + PSE 30 mg+ codeine 10 mg) or Pholeolix (APAP 150 mg, codeine 5 mg, PPA 12.5 mg)	**Population:** 217 children with cough (110 received PSE containing product). (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 110 (6 <12 yr)). **Safety Results:** There were no reports of deaths or SAEs. 54% reported drowsiness in the PSE containing group and all but one was of mild to moderate intensity. 14 subjects reported nausea (one was severe). **Conclusions:** The PSE combination product was tolerated.
Weippl G, Mauracher E (1983). *Pharmatherapeutica* 3(6):405-409.	Open, non-PBO-controlled study	Dosed 3 or 4 times daily with 2.5 or 5 ml of 'Disophrol Syrup' (1.5 mg dexbromphen-	**Population:** 30 children (**aged 5 – 12 years**) with a confirmed diagnosis of seasonal allergic rhinitis. (0 (0< 6mo), 0 (6mo<2yr), 1 (2<6 yr), and 29 (6 <12 yr). **Safety Results:** Incidence of adverse reactions was limited to one occurrence of extreme fatigue that lasted for 10 days, which did not necessitate termination of

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		iramine maleate + 30 mg PSE sulfate / 5 ml)	therapy. Vital signs were unaffected. **Conclusions:** The combination of DXBR/PSE in a syrup formulation (Disophrol) was well tolerated.
Weippl G (1984). *Clinical Therapeutics* 6(4):475-482.	Randomized, DB, comparative study	Antihistamine-decongestant-antitussive formulation (SCH 399: 0.5 mg AZA, 30 mg PSE, 10 mg DEX, t.i.d. or q.i.d., depending upon age) or with an antihistamine-expectorant formulation (DPH, AMM, SC, MTH t.i.d. or q.i.d., depending upon age) for 5 days.	**Population:** 56 children (**4 - 11 years**) presenting with symptoms of a common cold of 24 – 48 hours duration.* (29 received AZA+PSE and 26 DEX.) **Safety Results:** No adverse reactions were reported by subjects or observed by physicians. No clinically important vital signs were observed in either treatment group. **Conclusions:** The treatments were tolerated, no safety issues were identified.
Sakchainanont B, et al. Journal of the Medical Association of Thailand. 1990;73(2):96-101	DB, randomized PB)controlled study	CLEM fumarate (0.05 mg/kg/day twice a day), CPM maleate syrup (0.35 mg/kg/day, three times a day), or PBO.	**Population:** 150 patients (under 5 years of age) (48 received CPM*). **Safety Results**: There was no difference among groups with regards to slight drowsiness and sleepiness. Both antihistamine groups had not more side effects than the placebo group. **Conclusions:** The treatment was tolerated, no safety issues identified.
Hutton N, et al. (1991).	RCT	The antihistamine-decongestant drug	**Population:** 96 children, aged **6 months – 5 years** with upper respiratory symptoms consistent with a common cold.*

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Pediatric Pharmacology and Therapeutics 118(1):125-130.		(Dimetapp) contained BRP (4mg/5ml), PPA (5mg/5ml), and PE (5mg/5ml), PBO, or no medication, dosed according to the child's weight 3 times a day for 2 days.	**Safety Results:** Parents were asked if their children had any bad effects from the medicine. One child in the placebo group had loose stool, and one child in the drug group was reported to be hyperactive. A second child in the drug group was sleepier than usual. **Conclusions:** The treatment was tolerated, no safety issues identified.
Korppi M. *Acta Paediat Scand*.1991;80:969-71	DB, parallel group study	(1.5 mg/ml DEX), (1.5 mg/ml DEX and 0.2 mg/ml SAL) or PBO for 3 days. Dose was 5 ml TID for children < 7 and 10 ml TID for children > 7.	**Population:** 75 children (**1-10 years**). (49 received DEX or DEX + SAL.) **Safety Results:** Incidence of adverse events was low and equal in all groups. **Conclusions:** Incidence of adverse events was low and equal in all groups.
Taylor JA, et al. J Ped 1993;122:799-802.	RCT	1 dose at bedtime for 3 nights DEX+GUA, COD+GUA, PBO	**Population:** 141 doses in 49 pts age 18mo-12yr with nocturnal cough. **Safety Results:** Drowsiness occurred in 3 patients from the PBO group, and 3 patients from the DEX group. Diarrhea occurred in 3 patients from the PBO group and 1 patient from each the codeine and DEX groups. Hyperactive behavior was reported in 2 children receiving DEX. **Conclusions:** The study medications were tolerated. There was no safety signal.
Martinez-Gallardo F, et al.(1994). *Proceedings of the Western*	DB, PBO-controlled trial	PSE syrup (15 – 60 mg t.i.d., depending upon age), a suspension	**Population:** 65 children (**aged 2 – 16 years**) presenting with symptoms of a common cold. 30 received PSE or PSE+naproxen aged 2-12 yr (0 (0< 6mo), 0 (6mo<2yr), 6 (2<6 yr), and 24 (6 <12 yr)).

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Pharmacology Society 37:157-158.		combining PSE and naproxen (15 – 60 mg and 50 – 200 mg, respectively, t.i.d.), or PBO for 5 days	**Safety Results:** No side effects were reported. **Conclusions:** The treatment was tolerated, no safety issues identified.
Simons FE, Watson W. Journal of Pediatrics.1996; 129: 729-734. Gu X, et al. *J. Allergy Clin. Immunol.* 1996;97(1 pt. 3):199 (PK study)(abstract only)	In two sequential DB, parallel group, single dose studies	PSE, 30 or 60 mg, or PBO and 20 children received PPA, 20 or 37.5 mg or PBO.	**Population:** 41 children with allergic rhinitis (14 received PSE: (0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 14 (6 <12 yr)). **Safety Results:** Both doses of both decongestants increased the pulse rate, but this was only statistically significant at 4 hr after use of the PSE 60 mg. No significant increases in blood pressure occurred after use of either decongestant. **Conclusions:** The treatment was tolerated, no safety issues identified.
Tinkelman DG. et al. Pediatric Asthma Allergy & Immunology. Vol. 10(1)(pp 9-17), 1996.	Multicenter, randomized, parallel-group study evaluated the efficacy and safety of CTZ, in a single dose or divided doses, and CPM in.	CTZ 5 – 10 mg in a single dose (n=62), CTZ 5 – 10 mg in 2 divided doses (n=61) and CPM 2 mg TID (n=63) for 2 weeks.	**Population:** 188 pediatric subjects with SAR (63 received CPM: 0 (0< 6mo), 0 (6mo<2yr), 0 (2<6 yr), and 63 (6 <12 yr)). **Safety Results:** Most of the patients who experienced AEs reported only mild-to-moderate severity. AEs were reported by 33.6% of pts in the combined CTZ groups and 38.1% of the CPM group. The majority of AEs were mild to moderate in intensity. The most commonly reported AE for CTZ was abdominal pain in 12 of 125 (9.6%) pts, compared with 3 of 63 (4.8%) pts in the CPM group. Somnolence was reported in 5 of 63 (7.9%) CPM pts and 10 of 125 (8.0%) CTZ pts in both groups. When the CTZ groups were compared, somnolence was more common in pts taking 5 mg twice daily (13%) than in those taking 10 mg daily (3.6%). Fatigue was reported by 4.0% of pts in the combined CTZ groups compared with 6.3% in the CPM group. Nausea and headache occurred in 3.2% of CTZ pts; headache occurred in 6.3% and nausea in 1.6% of CPM pts. Only one subject in the CPM group withdrew due to an adverse

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			event. No clinically significant changes were in clinical laboratory tests were seen in this study. **Conclusions:** CTZ, given once daily or in divided doses twice daily, and CPM given 3 times daily for SAR in children aged 6-11 years was tolerated. Neither drug was associated with worsening of asthma.
Serra HA, et al. BR J Clin Pharmacol 1998;45: 147-150.	Randomized PBO controlled DB crossover	LOR (0.1 mg/kg) + PSE (1.2 mg/kg) twice daily for 2 weeks, and the other group received PBO. After a 7-day washout period, patients were shifted to the other treatment.	**Population:** 40 children (**aged 3 – 15 years**) with SAR.* (38 completed the trial and it is estimated 30 were 0<12yr.) **Safety Results:** One subject reported slight transient insomnia when receiving LOR + PSE. No changes were observed in vital signs or laboratory tests during the trial. **Conclusions:** The treatment was tolerated, no safety issues identified.
Jayaram. S. J Indian Med Assoc Vol 98 No.2, Feb 2000	Randomized DB study	Ascoril expectorant (SAL 1 mg, BRHX HCl 2 mg , GUA 50 mg, MTH 0.5 mg /5 mL) and other cough formula (DPH , AMM, SC, MTH/5 mL)	**Population:** 50 pediatric and adults patients* **Safety Results:** No serious adverse events were noted or reported in either group over the study period. **Conclusions:** The treatment was tolerated, no safety issues identified.

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Citation	Study Design	Dose/Duration	Study Populations, Results, Conclusions
Paul IM, et al. Clinical Therapeutics. 2004,Vol.26(9): 1508-1514 /Paul IM, et al. Pediatrics. 2004;114:e85-e90 Yoder KE, et al. Clin Pediatr. 2006;45:633-640	Double-blind, PBO-controlled trial.	DEX doses with children aged 2-5 years receiving 7.5 mg per dose (0.35 to <0.45 mg/kg), 6-11 receiving 15mg per dose (0.45 to <0.60 mg/kg), and children 12-18 receiving 30 mg per dose (0.60 to 0.94 mg/kg).	**Population:** 33 patients (19 girls, 14 boys), ages 2-18* with cough attributed to URI. (Estimated 22 were children 0<12yr.) **Safety Results:** The most common reported adverse event was hyperactivity (LD; 2, MD; 3, HD;1), but there was no statistically significant between-group differences in the occurrence of any adverse event. Other adverse events included insomnia, stomachache/ nausea, and dizziness. In total, there were 3 adverse events in the LD group, 4 in the MD group, and 6 in the HD group. **Conclusions:** There were no statistically significant between-group differences in the occurrence of any adverse event.
Merenstein (2006) *Arch Pediatr Adolesc Med. 160:707-712*	Randomized, DB, controlled clinical study	DPH 1 mg/kg once daily for 1 wk	**Population:** 44 children with frequent night time awakenings (22 received DPH: (0 (0< 6mo), 22 (6mo<2yr), 0 (2<6 yr), and 0 (6 <12 yr). **Safety Results:** There were no deaths and no SAEs reported. No parents reported adverse effects that caused them to stop study participation early. One patient in the DPH group acquired hand, foot, and mouth disease during the study and stopped after 5 days of intervention. Investigators and the data safety monitoring board judged that this was not related to study intervention. Two other children in the placebo group had mild adverse effects, one with hyperactivity and the other with diarrhea, and one in the DPH group also was reported as having hyperactivity. All conditions were reported by the parents to be mild. **Conclusions:** The treatment was tolerated, no safety issues identified.

*Not enough information to classify subjects into more finely divided age breaks: 0<6mo, 0<2 yr, 2<6 yr, 6<12 yr.)

Key

APAP=acetaminophen **BRM**=brompheniramine **CLEM**=clemastine **CPM**=chlorpheniramine **DEX**=dextromethorphan
DPH=diphenhydramine **EPH**=ephedrine **GUA**= Guaifensin **IBU**=ibuprofen **LOR=Loratadine**
PE= phenylephrine **PSE**=pseudoephedrine **PPA** =phenylpropanolamine **PBO**=placebo
DB=double-blind **NAR**=nasal airway resistance **OL**=open label

Table 5.9 Safety Data from Prospective Clinical Trials in Children
Company Sponsored, Published Literature and Post Marketing Studies

Table 3. Post Marketing Studies

Citation	Study Design	Dose/Duration	Study Populations, Safety Results, Conclusions
Porta et al. (1986) *Annals of Allergy* 340-342.	Post Marketing Surveillance from Group Health Cooperative of Puget Sound 1976 - 1983	PSE varies doses	**Population:** 100,000 filled 243,286 scripts for subjects < 65 yrs representing 3,649,290 person days at risk for hospitalization. (81,965 scripts for 0-19 yr age subset) **Safety Results:** 246 hospitalizations within 15 days of PSE all but one ruled out. One was 22 mo old female with seizure that lasted one minute. Causality was considered remote. **Conclusions:** Provides reassurance that PSE is safe as it is used in the general medical practice.
Wezorek C et al. (1995) *Clin Tox* 33(5):554 (abstract)	Prospective Study to determine Toxic Dose in Children.	PSE at doses up to > 180 mg	**Population:** 140 Children < 6 yrs who ingested PSE only (101 ingested 30-180 mg; remaining > 180 mg. **Safety Results:** Drowsiness was 21.7% in the 30-180 mg and 15.4% in the > 180 mg group. Mild hyperactivity was 6.9% in the 30-180 mg group and 15.4% in the > 180 mg group. **Conclusions:** PSE produced mild symptoms even at high doses.

Key

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Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to FDA Questions

Module 2 of 3

Part 2

Supplemental Data

Module 2 Part 1

1. CHPA Briefing Book for Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee, October 18-19, 2007. Submitted to FDA Docket No. 2007P-0074.

Module 2 Part 2

2. Analysis of Pediatric Nonfatal Reports Coded as Serious from the McNeil Post-marketing Adverse Event Database. CHPA Pediatric Task Force, December 2, 2008
3. Pediatric fatalities associated with over-the-counter (nonprescription) cough and cold medications. Final Report by Rocky Mountain Poison and Drug Center, November 21, 2008
4. Pediatric Safety Data From Clinical Studies on OTC Cough/Cold Medicines. CHPA Pediatric Task Force, December 2, 2008

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Module 2 - Section #2

Analysis of Pediatric Nonfatal Reports Coded as Serious from

The McNeil Post-marketing Safety Database

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

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1 SAFETY OF OTC COUGH AND COLD MEDICINES IN CHILDREN

1.1 Introduction

On October 18, 2007, at the Joint Meeting of the Nonprescription Drugs and Pediatric Advisory Committee Meeting on Pediatric Cough and cold Medicines, McNeil Consumer Healthcare (McNeil) presented an analysis of the pediatric nonfatal reports, coded as serious from their post-marketing safety database [1]. This analysis included reports where products containing the following cough and cold ingredients: chlorpheniramine, dextromethorphan, diphenhydramine, psuedoephedrine, and phenylephrine were reported as suspect medications. Reported cases of fatalities received from the Consumer Healthcare Products Association (CHPA)-member companies, including McNeil were reviewed and presented separately by the Rocky Mountain Poison and Drug Center [1] and are not included in this review.

Based on this analysis it was concluded that reports involving over-the-counter (OTC) cough and cold ingredients which were coded as serious, from accidental ingestion, therapeutic use, and overdose are very rare and when used as directed and administered at therapeutic doses, OTC cough and cold medicines, appear to be well tolerated.

1.1.1 McNeil Post-Marketing Safety Database

The McNeil post-marketing safety databases contain adverse event data from the 1980s to present and include data on brands such as Children's Benadryl®, Children's Tylenol®, Children's Motrin® Cold, Pediacare®, and Children's Sudafed®. The adverse event data was retrieved from multiple databases and was received over 27 years. The definitions used to categorize and code reports have varied over time, and there is heterogeneity of the data. In order to use this dataset in a more meaningful way to guide public health decisions, it was necessary to perform a case level review of the reports that were coded as "serious" and re-categorize them using standard definitions.

1.2 Serious Non-fatal Case Review

The case level review classified the reported reason for exposure, the reported dose ingested and the clinical effects, if any, which were reported following exposure. This analysis aided in determining if a patient in a report coded as serious developed clinical effects and if so, the seriousness of those clinical effects.

1.2.1 Inclusion/Exclusion Criteria

This review included all reports coded as serious with a nonfatal outcome in children less than 12 years of age who ingested a pediatric or adult product containing OTC cough and

cold ingredients. Products containing the following cough and cold ingredients, either as a single ingredient or combination ingredient product were included: chlorpheniramine, dextromethorphan, diphenhydramine, psuedoephedrine, or phenylephrine. Reports were excluded if the cough and cold medication was not ingested orally by a child less than 12 years of age (e.g. topical, intravenous, exposure-in utero) or if a child ingested a product labeled for topical use containing a cough and cold ingredient (e.g. diphenhydramine).

1.2.1.1 Exposure Types

All reports were individually reviewed and categorized either as accidental ingestion, use for a labeled indication, or other according to the following definitions. Reports involving an accidental ingestion involved a child getting into a cough and cold medicine on their own, when the medicine was not appropriately kept out of their reach. Reports categorized, as use for a labeled indication included the use of a cough and cold medicine for the treatment of cough and cold symptoms. If another reason for exposure was not specifically mentioned, the report was classified as use for labeled indication. The third category, other, included two categories: malicious intent and use for an unlabeled indication. When it was reported that there was suspected or confirmed abuse, reports were categorized as malicious intent and when a cough and cold medicine was administered for a non-cough and cold indication, such as sedation, reports were classified as use for unlabeled indication.

1.2.1.2 Reported Dose Category

The reported dose for each case was reviewed and categorized as a therapeutic dose, an overdose, or dose unknown. A therapeutic dose was defined as less than or equal to the recommended single dose when a single dose was administered or less than or equal to the maximum daily recommended dose when more than one dose was administered. The recommended dosing was based upon weight or age of the child, and the labeled dose. In the event a dose was not labeled for a particular age in either the package-label or professional labeling, an extrapolated dose based on age was used. For example, Table 1-1. illustrates the dosing used to determine the dose category for psuedoephedrine.

Table 1-1. Pseudoephedrine Dosing to Determine Dose Category: Labeled and Extrapolated

Age	Maximum Single Dose (mg)	Maximum Daily Dose (mg)
0 to under 4 months	3.75	15
4 to under1 2 months	7.5	30
12 under 24 months	11.25	45
2 to under 6 years	15	60
6 to under 12 years	30	120

1.2.1.3 Reported Severity of Clinical Effects

Although all of the reports in this analysis were coded as "serious" based on regulatory definitions and the interpretation of the reviewer at the time the report was received, not all children experienced clinical effects. For this reason, we reviewed each case to determine if clinical effects were reported. Reports in which no symptoms were reported were categorized as asymptomatic. When symptoms were reported, the symptoms were categorized as mild effects, moderate to severe effects or unable to assess/unrelated. In reports in which both mild effects and moderate to severe effects were reported, the symptoms were categorized as moderate to severe. A report categorized as mild effects had signs or symptoms reported, but these signs or symptoms were minimally bothersome with no residual disability. Some examples of mild effects were mild sedation (somnolence), rash, nausea, pupillary changes, nervousness, hyperactivity, mild allergic reactions (rash, swelling, itching), and abdominal pain. Reports categorized as moderate to severe effects involved signs or symptoms that were more pronounced, more prolonged, and more systemic in nature than the mild effects. Some examples of moderate to severe effects included moderate to severe sedation (lethargy), tachycardia, hypertension, hallucinations, disorientation, seizures, serious allergic reactions (dyspnea and respiratory compromise), dysrhythmias, fever, and chest pain. Some cases were categorized as unable to assess if it was unclear if the symptoms developed as a result of the medication. Examples included: worsening of the following: fever, allergic reaction, cough or development of infection. A few cases were categorized as unrelated symptoms if the symptoms were unlikely related to the medication. Examples of unrelated symptoms included: urinary tract infection, osteomyelitis, necrotizing fasciitis, and septic arthritis.

1.2.2 Product Exposure in the Marketplace

The dataset contained reports representing approximately 38% [2] of all pediatric cough and cold medicines distributed in the United States. In order to provide context around the product exposure for this specific dataset, there are between 500 and 600 million doses of pediatric OTC cough and cold medicines distributed each year [3]. Each week, a pediatric over-the counter cough and cold medicine is used by approximately 12% of children under6 years of age and by 8.5 % of children 6 to under 12 years of age [5]. Table 1-2 shows the distribution of pediatric cough and cold medicine use and the exposure in any given week. The age distribution was estimated based on use of OTC medicines for cough and cold by children in the United States from the Slone Epidemiology Center and United States census data from 2000. Eighteen percent of all pediatric cough and cold medicines are used by children under 2 years of age, 39% of all pediatric cough and cold medicines are used by children age 2 to under6 years, and 43% of all pediatric cough and cold medicines are used by children age 6 to under12 years [4, 5].

Table 1-2. Use of Pediatric Cough and cold Products by Age Group: Slone Survey 1998-2007

Distribution Estimates [4, 5]	Under 2 years	2 to under 6 years	6 to under 12 years
Exposure in any given week	12%	12%	8.5%
Pediatric cough and cold medicine use	18%	39%	43%

1.2.3 Results

A total of 20,111 adverse event reports were identified. Of the 20,111 reports, 19,475 reports were coded as non-serious, 562 reports were coded as serious, and 74 reports had a fatal outcome. The breakdown by age for these reports is shown in Table 1-3 and Table 1-4. Table 1-3 shows the percentage of total reports and also shows the breakdown of pediatric cough and cold medicine use. When considering the distribution of cough and cold medicine use, reports in children under 2 years within the dataset appear to be significantly over-represented. While 18% of the use of cough and cold medicines occurs in children under 2 years, 33% of the reports occur in this age group. In comparison, 39% of the use of cough and cold medicines occurs in children 2 to under 6 years and 49% of the reports occur in this age group. Further analysis of the data revealed some potential reasons why there appears to be overrepresentation of reports for children in these age groups.

Table 1-4 summarizes all of the reports in children under 12 years of age in the dataset. Of all the reports in this database, 96.8% were coded as non-serious. There were a total of 74 fatal reports. All of the fatal reports were submitted to and reviewed by an expert panel and were analyzed and presented by the Rocky Mountain Poison and Drug Center [1]. There were 562 reports that were coded as serious. Table 1-5 shows that reports coded as serious represent a relatively small percentage across all age groups. Of the 562 reports coded as serious, 194 (34%) had no clinical effect reported and 110 (19.6%) had only a mild clinical effect reported. There were 218 reports over the 27-year period in which a moderate to severe clinical effect was reported.

Table 1-3. Percent of Pediatric Reports from McNeil Post-marketing Safety Database and Percent of Cough and cold Medicine Use By Age Group: Reports and in Children under 2 Years are Overrepresented in Comparison to Distribution of Product Use

Case Reports	Under 2 years	2 to under 6 years	6 to under12 years	Age Unknown
N	6550	9907	3089	565
% of total reports	**33%**	49%	15%	3%
Pediatric cough and cold medicine use	**18%**	39%	43%	

Table 1-4. McNeil Post-marketing Safety Database: Distribution of Reports by Seriousness for Children under 12 Years: 1980 - June 2007

Reports coded as	N	%
Non-serious	19,475	96.8
Serious	562	2.8
Fatal	74	0.4
Total	20,111	100

Table 1-5. McNeil Post-marketing Safety Database: Percent of Reports Coded as Serious by Age Group: 1980 – June 2007

Case Reports	Under 2 years	2 to under 6 years	6 to under 12 years	Age Unknown
All reports (N=20,111)	6550	9907	3089	565
Reports coded as serious (N=562)	123	339	80	20
% all reports coded as serious	**1.9%**	**3.4%**	**2.6%**	**3.5%**

1.2.3.1 Accidental Ingestion

Fifty-four percent of the reports coded as serious were categorized as accidental ingestion. These reports described children who gained unsupervised access to either an adult or

pediatric cough and cold medicine on their own. In these cases, the medicine was not appropriately kept out of the reach of a child. The majority (80%) of these accidental ingestions involved an adult product, 19% involved a pediatric product, and in 1% of the cases it was unknown if the product was a pediatric or adult product.

Table 1-6 shows the number of reports coded as serious, number of reports categorized as accidental ingestion and the percentage of serious reports that were categorized as accidental ingestion by age group. Accidental Ingestion is more common in children 2 to under 6 years and is the leading cause for reports coded as serious within this age group. In children 2 to under 6 years, 70% of all the reports coded as serious were unrelated to use of a cough and cold medicine for the treatment of cough and cold symptoms. In children under 2 years of age, 41% of all the reports coded as serious were also unrelated to the therapeutic use of a cough and cold medicine.

Table 1-6. McNeil Post-marketing Safety Database: Percent of Reports Coded as Serious Involving Pediatric Accidental Ingestion by Age Group: 1980-June 2007

	Under 2 years	2 to under 6 years	6 to under 12 years
Serious reports (N=562)	123	339	80
Accidental ingestion (N=301)*	50	237	6
% of serious reports	41%	70%	8%

* 8 (3%) reports, age of child unknown

Accidental ingestions of cough and cold medicines are usually not associated with clinical effects. In the 2 to under 6 age group, 56% of the accidental ingestions that were coded as serious, did not result in any clinical effects being reported. In this same age group, 26% of the accidental ingestions resulted in a mild effect and 18% resulted in a moderate to severe effect. In reports where the dose could be determined, all of the reports of accidental ingestion were from a reported overdose.

Table 1-7. McNeil Post-marketing Safety Database: Percent of Reports Coded as Serious Involving Pediatric Accidental Ingestion by Age Group and Clinical Effect Severity: 1980- June 2007

	Under 2 years	2 to under 6 years	6 to under 12 years
Accidental ingestion (N=301)*	50	237	6
No clinical effects reported	29	133 (56%)	4
Mild AEs/clinical effects	11	61 (26%)	0
Moderate to severe AEs/clinical effects	10	43 (18%)	2

* 8 (3%) reports, age of child unknown

1.2.3.2 Use for Labeled Indication

Two hundred and thirty-nine (239) reports were categorized as use for labeled indication. It was presumed in these cases that the cough and cold medicine was administered to a child for treating cough and cold symptoms. When cough and cold medicines are used for the labeled indication, considering distribution of product use, there is an over-representation of reports coded as serious in children under 2 years of age (Table 1-8). While 18% of the use of cough and cold medicines occurs in children under 2 years of age, 29% of the reports coded as serious with use for a labeled indication occur in this age group. In comparison, 39% of the use of cough and cold medicines occurs in children 2 to under 6 years and 41% of the reports coded as serious occur in this age group.

Table 1-8. McNeil Post-marketing Safety Database: Percent of Reports Coded as Serious with a Labeled Indication and Percent of Cough and cold Medicine Use By Age Group

Case Reports	Under 2 years	2 to under 6 years	6 to under 12 years
Use for labeled indication (N=239)*	69	97	65
% of serious reports with use for labeled indication	**29%**	41%	27%
Pediatric cough and cold medicine use [4,5]	**18%**	39%	43%

* 8 (3%) reports, age of child unknown

In 138 of the reports categorized as use for labeled indication, it was reported that a therapeutic dose was administered to the child. In 53 of the reports, it appeared based on

the data, that an overdose was administered. In 48 reports, dosing information was not sufficient to determine whether the child received a therapeutic dose or overdose.

Table 1-9 shows dosing categories for reports categorized as use for a labeled indication by age group. Doses are classified as either therapeutic dose or other. Within therapeutic dose, there are three categories listed: dosing information that is listed on the OTC label, professional dosing listed in the Code of Federal Regulations Part 341 - Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products For Over-The-Counter Human Use [6], or extrapolated dose [Section 1.2.1.2]. The medical literature and other sources provide extrapolated therapeutic doses for cough and cold medicines for children under 2 years of age. In the “other” category, overdose or reports where the dose was unknown are listed. Prior to the time of this analysis, for OTC cough and cold medicines, there was no dose on the label for children under 2 years of age. The label stated: “Consult a doctor” or “ask a doctor”. For cough and cold medicines that contain an antihistamine, there is no dose on the label for children under 6 years of age. Therefore, by definition, these children could not have received a labeled therapeutic dose. Of the 69 doses administered to children under 2 years of age, 34 were determined to be a therapeutic dose based upon extrapolation. In no report was it documented how caregivers may have arrived at this extrapolated dose. It is unknown whether the label instructions were followed and a doctor was consulted, or whether the dose was determined by other means.

At the time of this analysis, for children 2 to under 6 years of age, there was a specific dose in the OTC label for cough and cold medicines which did not contain an antihistamine. In 17 of the 97 reports, use of a labeled therapeutic dose was documented. When a cough and cold medicine contained an antihistamine, a therapeutic dose for children 2 to under 6 years of age was based upon professional dosing as outlined in the Code of Federal Regulations Part 341 - Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products For Over-The-Counter Human Use [6]. In 35 reports, the dose administered was reported to be a therapeutic dose based upon monograph professional dosing. Similar to children under 2 years, it is unknown whether the label instructions were followed and a doctor was consulted or whether the dose was determined by other means.

In all of the 18 reports of overdose in children under 2 years of age, there was no specific dose on the OTC label. In 24 of the 27 reports of overdose in children 2 to under 6 years of age, there also was no specific dose on the OTC label.

Table 1-9. McNeil Post-marketing Safety Database: Number of Reports Coded as Serious with a Labeled Indication by Age Group and Dosing Category

Use for labeled indication (N=239)*	Under 2 years (n=69)	2 to under 6 years (n=97)	6 to under 12 years (n=65)
Therapeutic dose			
Per OTC label	No dose on label	17	50
Monograph/professional	No professional monograph dose	35	NA
Extrapolated	34	NA	NA
Other dose			
Overdose	18	27	7
Unknown	17	18	8

* 8 (3%) reports, age of child unknown

1.2.3.2.1 Root Causes of Pediatric Overdose - Labeled Indication

The reports that were categorized as overdose when used for a labeled indication were reviewed to attempt to understand some of the root causes of overdose in these children. Table 1-10 lists the reported errors and frequency by age group. Some reasons for overdose include, administering an adult cough and cold medicine to a child, administering multiple products containing the same active ingredients at the same time, and administering medicines too frequently. The most common root cause for overdose in children under 2 years of age and in children 2 to under 6 years of age is incorrect dosing. Although the reason for incorrect dosing could not be determined from the case level review, there are far fewer reports of incorrect dosing in children 6 to under 12 years when a specific dose for children of this age is listed on the OTC label. For all of the 13 reports in children under 2 years of age and for the 20 of the 24 reports in children 2 to under 6 years where an incorrect dose resulted in an overdose, there was no specific dose on the OTC label for children in these age ranges.

Table 1-10. McNeil Post-marketing Safety Database: Number of Reports Coded as Serious with a Labeled Indication: Root Cause of Pediatric Overdose

Reported errors	Under 2 years (n=18)	2 to under 6 years (n=27)	6 to under 12 years (n=7)
Adult product to child	0	1	1
Multiple products containing same ingredients	4	1	0
Incorrect frequency of dosing	1	1	0
Incorrect dose	13	24	6
No specific dose on label	13 of 13	20 of 24	

Using data from the case level review and product distribution data, reporting rates were calculated (Table 1-11). Reporting rates were calculated by dividing the number of reports that were received from January 2000 through June 2007 by consumption units per million sold in the same time period. The percentages from the distribution of pediatric cough and cold use (Table 1-2) were applied to the dosing units in order to estimate the exposure for the specific age groups. The reporting rates for a report coded as serious, regardless of whether an actual adverse clinical event was reported, are listed for each age range and each reported dose ingested per 1 million consumption units. Considering the exposure data, the reports coded as serious with the use of a cough and cold medicine for a labeled indication are very rare.

In this dataset, for children under 2 years of age, use of an OTC pediatric cough and cold medicine for a labeled indication was associated with a report coded as serious at a rate of 0.073 times per 1 million doses distributed. The rates for children under 2 years of age for every dose category are higher than the rates in other age groups. Also shown are the reporting rates for reports coded as serious per 1 million doses distributed when the specific dose was and was not on the OTC label. Whenever the dose was not on the over-the counter label, the reporting rates were higher than when the dose was on the label. The highest reporting rate when the dose was not on the label was for children under 2 years of age.

Table 1-11. McNeil Post-marketing Safety Database: Reports Coded as Serious with Labeled Indication: Reporting Rate per 1M Consumption Units of Pediatric OTC Cough and Cold Medicines by Age Group and Dose Category: January 2000 – June 2007

Use for labeled indication	Under 2 years n=55 (0.073)	2 to under 6 years n=68 (0.042)	6 to under 12 years n=51 (0.028)
Therapeutic dose (N=117)*	0.041	0.025	0.025
Overdose	0.019	0.010	0.002
Unknown dose	0.013	0.007	0.002
Dose on label	NA	0.011	0.028
Dose not on label	0.073	0.031	NA

* 6 reports, age of child unknown

1.2.4 Conclusion

There is a long history of use of OTC cough and cold medicines in children. This analysis of the post-marketing databases, representing 27 years of data supports findings from the clinical trial database that when used as directed and administered at therapeutic doses, OTC pediatric cough and cold medicines, are well tolerated. When the post-marketing data is reviewed in context of use, reports coded as serious, from accidental ingestion, from therapeutic use, and from overdose are very rare. In children from 2 to under 6 years of age, accidental ingestions account for the vast majority of reported serious adverse events. The development of moderate to severe clinical effects following accidental ingestions is unusual. Therapeutic doses in children 2 to under 12 years of age appear to be well-tolerated. There is an over-representation of reports coded as serious in children under 2 years of age. While most caregivers administer cough and cold medicines appropriately, rare instances of misuse leading to overdose occur, especially in children under 2 years of age. It appears that a lack of a specific dose on the OTC label for age ranges in which over-the counter cough and cold medicines may be used, may be associated with incorrect dosing and overdose.

When used as directed, OTC pediatric cough and cold medicines appear to be well tolerated.

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Pediatric fatalities associated with over-the-counter (nonprescription) cough and cold medications

FINAL REPORT

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Executive Summary

The use of nonprescription cough and cold medicines is widespread, but their use has been sporadically associated with severe toxicity and death. We evaluated the role of these medications in pediatric fatalities and identified factors that contributed to the death. Fatalities that involved a child under the age of 12 years and mentioned a cough and cold ingredient were obtained from five sources. An independent panel of eight experts (pediatrics, pediatric critical care, pediatric toxicology, clinical toxicology, forensic toxicology, forensic pathology) used explicit definitions to assess the causal relationship between medication ingestion and death. Contributing factors were identified.

Of 189 cases included, 118 were judged possibly, likely, or definitely related to a cough and cold ingredient. Of these 118 cases, 103 involved a nonprescription drug while 15 cases involved a prescription medication alone. Of 103 cases associated with nonprescription drugs, the evidence indicated that 88 involved an overdosage. A dosage could not be assessed in the remaining 15 cases. Several contributing factors were identified: age less than 2 years, use of the medication for sedation, use in a daycare setting, use of two medicines with the same ingredient, failure to use a measuring device, product misidentification, and use of a nonprescription product intended for adult use. All cases that occurred in a daycare setting involved a child under age 2 years.

In our sample, pediatric fatalities due to nonprescription cough and cold medications were uncommon, involved overdose and primarily affected children less than 2 years of age. Their intent of caregivers appears to be therapeutic to relieve symptoms in some cases and nontherapeutic to induce sedation or to facilitate child maltreatment in other cases.

Introduction

The increasing use of nonprescription (over-the-counter) cough and cold medicines is a worldwide phenomenon. Sales of these products is approximately $3.5 billion annually in the United States.(1) Approximately four million children under the age of 12 years are treated with nonprescription cough and cold products each week in the United States.(2)

Cough and cold products have been sporadically associated with severe toxicity and death in children. The American Association of Poison Control Centers (AAPCC) reported a total of 64,658 exposures to cough and cold products in children under the age of 2 years in 2005; of these, 28 (0.04%) were associated with a major effect or death.(3) Recent reports of death associated with these products have brought this issue to the attention of regulatory bodies.(4)

The United States Food and Drug Administration (FDA) convened an external advisory committee to evaluate the efficacy and safety of nonprescription cough and cold products. On October 19, 2007 the committee recommended that the use of these medications be prohibited in children under the age of 6 years. Despite the advisory committee's recommendations, a poll performed by National Public Radio, the Kaiser Family Foundation and the Harvard School of Public Health after the recommendation reported that 20% of parents with children under the age of 2 years and 30% of parents with children 2 to less than 6 years of age plan to use cough and cold medicines for their children.(5)

A risk evaluation of the use of cough and cold products in children is needed, but has been difficult because the information publicly available consists of a small number of case reports and retrospective case series. To evaluate the role of nonprescription cough and cold medications associated with fatal cases, an expert panel was convened to compile all available pediatric fatalities associated with cough and cold medications, assess the causal relationship to the medications involved, estimate the dose involved, and identify factors contributing to the poisoning.

Methods

Case ascertainment and abstraction

The panel assessed all reported pediatric fatalities that could be gathered from five sources (Figure 1): the National Poison Database System (NPDS) of the American Association of Poison Control Centers (January 1983 through June 30, 2007), adverse event reports submitted to the major manufacturers of nonprescription cough and cold products (1980-2007), the FDA briefing materials for its advisory committee meeting on October 18-19, 2007 (6), a Citizen Petition to FDA submitted March 1, 2007 (6), and the medical literature (1950-2007). The

medications evaluated included the most commonly used nonprescription cough and cold ingredients: antihistamine (brompheniramine, chlorpheniramine, diphenhydramine, doxylamine), antitussive (dextromethorphan), expectorant (guaifenesin), and decongestant (pseudoephedrine, phenylephrine). Because the searches were based on ingredient, reports involving prescription medications were also identified. Cases involving prescription medications were included in the evaluation process because they often involved both nonprescription and prescription medications and helped characterize the toxicity of the individual components.

The following medical literature databases were searched: MedLine (1950 to July 2007) using Ovid and PubMed, EMBASE Drugs and Pharmacology (1980 to 3rd Quarter 2007), and International Pharmaceutical Abstracts (1970 – July 2007). The search was conducted by querying each drug separately, limiting to human and English language, and then combining with death using the Boolean operator AND drug name: brompheniramine, chlorpheniramine, dextromethorphan, diphenhydramine, doxylamine, guaifenesin, phenylephrine, and pseudoephedrine.

From each source, a case was included if the event occurred in the United States (US), the age of the subject was less than 12 years, the outcome was death, and one or more of the eight cough and cold ingredients of interest were identified by history or at postmortem analysis. There were numerous duplicate cases, which were combined to present a complete record of the event to the expert panel. Each fatal case was first independently abstracted by two trained abstractors that were not involved in the consensus process. The abstractors were non-medical personnel that made no medical judgments on the cases, but simply evaluated the case for inclusion and organized the data in a systematic fashion across disparate data sources. The abstracted fields included date of death, case source, demographics, product names, individual active ingredients, dose, duration of exposure, drug concentration (antemortem and postmortem), concomitant medical conditions, and results of scene investigation. Disagreements were resolved by discussion with their supervisor. When information was inconsistent, all reported data was captured and the panel was responsible for determining how the inconsistent information affected the interpretation of the case. The study was exempted from review by the Colorado Multiple Institutional Review Board.

Consensus panel

The panel was formed of a non-voting moderator and eight experts in the fields of pediatrics (IP, RK), pediatric critical care medicine (WB), and pediatric toxicology (BR, GB, WB) as well as clinical toxicology (AM, BR), forensic pathology (DW) and forensic toxicology (RP). Selection of panel members was based on evidence of previous research and clinical experience involving the use of cough and cold preparations in children. The panel reviewed the case abstract

as well as all source materials on each case individually prior to the meeting. All decisions by the panel were formed during one face to face meeting and one additional conference call. Panel members were asked to base their decisions on the entire body of information available for each case. Each case was then debated by the group until consensus was reached.

The panel classified each case using explicit definitions to assess the causal relationship:

- *Definitely related* to medication: History of ingestion or drug concentrations consistent with exposure, clinical course consistent with exposure, and no other cause of death evident.
- *Likely related*: History of ingestion or drug concentrations may be consistent with exposure, clinical course consistent with exposure, other cause of death possible, drug may have been secondary cause of death.
- *Possibly related*: History or drug concentrations may be consistent with exposure, clinical course unknown, other cause of death possible or unknown, drug may have been secondary cause of death.
- *Unlikely related*: History of ingestion or drug concentrations may be consistent with exposure, clinical course inconsistent or unknown, other cause of death likely.
- *Definitely not* related: History of ingestion or drug concentration concentrations not consistent with exposure, clinical course inconsistent or unknown, other cause of death evident
- *Unable to Determine:* Not enough case detail was available to evaluate relationship of drug to death

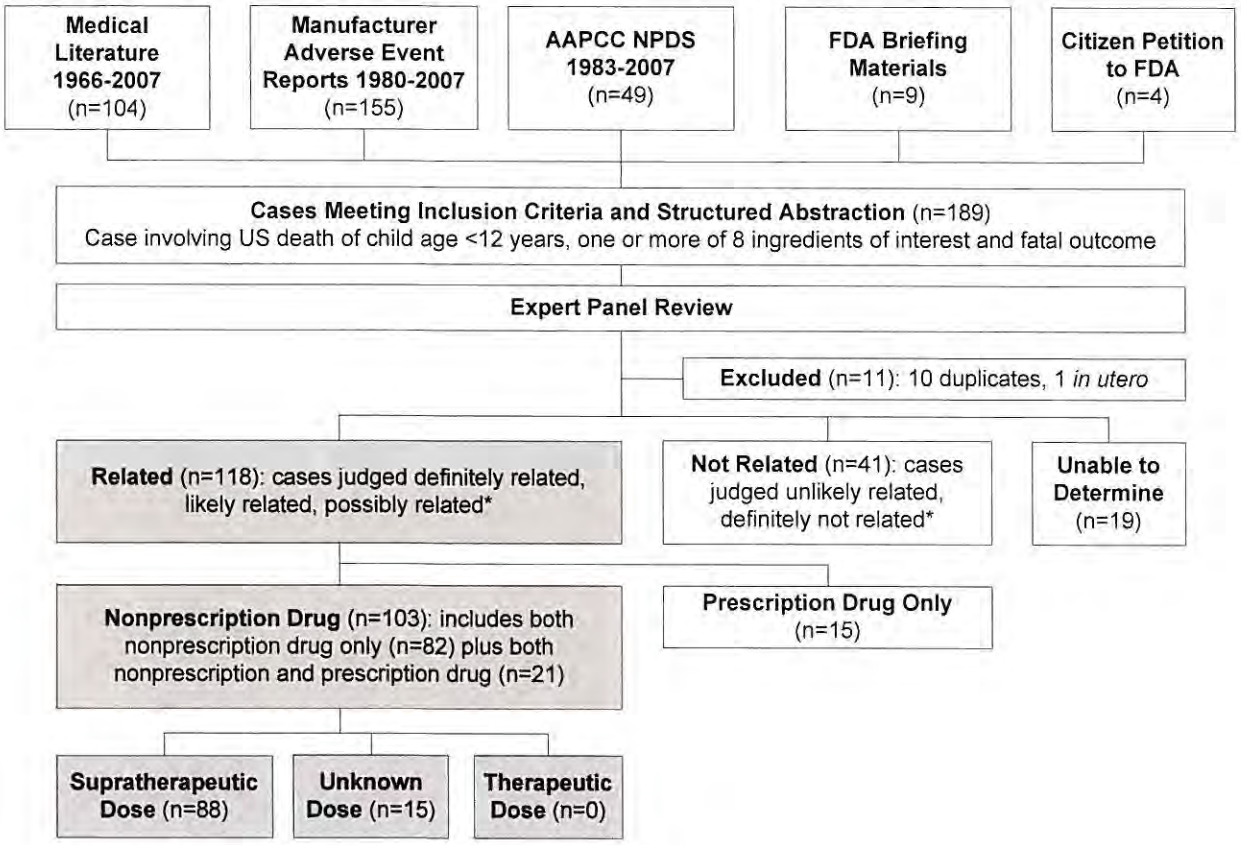
All cases assigned to the categories of possibly related, likely related, or definitely related were included as "related" for further analysis.

The panel also categorized the dose involved (therapeutic, supratherapeutic, unable to determine). To form this decision, the panel considered clinical information such as the medical history and blood concentrations performed before death and forensic information scene investigation, autopsy findings, postmortem drug concentrations and the medical examiner's assessment of the cause and manner of death). Full information was not available for all cases. The panel also identified the person that likely administered the medication (adult, child, unable to determine), the intent of administration (therapeutic intent, non-therapeutic intent, unable to determine), and identified any other factors that contributed to the incident. The term non-therapeutic was defined as the documented use of the medication for reasons other than the treatment of cough and cold symptoms (e.g. sedation). A child finding medication while exploring their environment was categorized as child administered.

Results

A total of 189 US deaths in children less than 12 years of age were identified by the search strategy. (4,7-29) The panel excluded 11 cases (Figure 1). Of the remaining 178 cases, 41 were judged "unlikely related" or "definitely not related" and there were 19 cases in which the causal relationship could not be assessed. The net result was 118 cases in which the panel concluded that a relationship between the cough and cold ingredient and the fatality was at least possible. Of these 118 cases, 33 (28%) were judged definitely related, 33 (28%) were likely related, and 52 (44%) were possibly related. Cases judged not related typically included both an obvious alternative cause (e.g. shock with positive blood culture) and a time course inconsistent with death from a cough and cold ingredient.

Figure 1. Disposition of fatal cases considered by expert panel



*See methods section for definitions
AAPCC NPDS – American Association of Poison Control Centers National Poison Data System
FDA – United States Food and Drug Administration

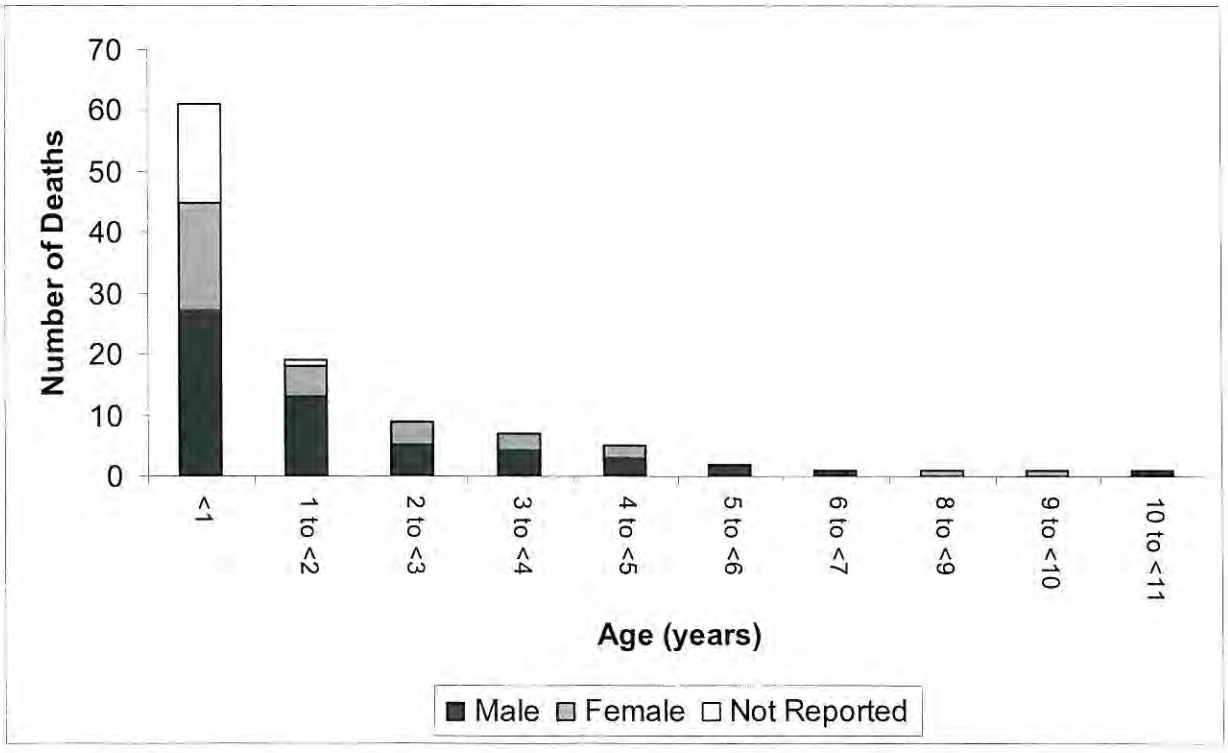
Of the 118 cases judged to be related to a cough and cold ingredient, 82 cases involved a nonprescription medication alone, 21 cases involved exposure to both a nonprescription and prescription medication and the remaining 15 cases involved only a prescription medication. Prescription medications typically

included an opioid (e.g. hydrocodone, codeine) or prescription antihistamine (e.g. promethazine, carbinoxamine) in addition to a nonprescription ingredient. Drugs where the prescriptive status could not be determined were placed in the nonprescription drug category.

The 82 cases involving a nonprescription drug alone were combined with 21 cases (total 103 cases) involving both a nonprescription drug and a prescription drug for further analysis. Since many cough and cold products contain more than one ingredient, these 103 cases involved a total of 162 index drug mentions judged as at least possibly related. Three drugs accounted for most mentions: pseudoephedrine (n=45), diphenhydramine (n=38) and dextromethorphan (n=36). The remaining mentions involved chlorpheniramine (n=17), brompheniramine (n=13), doxylamine (n=7), and phenylephrine (n=6). There were no mentions of guaifenesin judged to be related to death.

Age at the time of death ranged from 28 days to 10 years. When stratified by age groups defined by FDA-approved labeling, 77 (75%) cases involved a child under the age of 2 years, 22 (21%) involved a child 2 to less than 6 years of age and 4 (4%) involved a child 6 years to less than 12 years of age (Figure 2). Male children were involved in 53 (62%) of 86 cases where the gender was reported. Most of the 17 cases with unreported gender occurred in children less than 2 years of age.

Figure 2. Age and gender distribution in fatal cases judged related to a nonprescription cough and cold medication (n=103)



The site of exposure (e.g. child's home, daycare, home of baby sitter, or healthcare facility) was reported in 59 of the 103 cases. For cases in which the site was reported, the medication was administered in the child's home in 45 cases (76%), a daycare facility or home of a babysitter in 12 cases (20%), and a health care facility in 2 cases (3%). Characteristics of the daycare facility (e.g. licensure) could not be determined. All cases occurring in a daycare facility or babysitter's home involved a child under the age of 2 years.

The panel concluded that the child received a supratherapeutic dose in 88 of 103 cases. In the remaining 15 cases, the panel concluded the information available was insufficient to estimate dose (Figure 1). In 38 of 103 cases, the medication contained multiple cough and cold ingredients. In 18 cases, more than one product containing cough and cold ingredients was involved. The number of doses administered in each case was reported in only 18 cases and was not analyzed further.

Of the 103 nonprescription medication cases, the person administering the medicine was an adult in 79 (77%) cases, a child (self-administered) in 18 (17%) cases, and was not identified in 6 (6%) cases. The 79 cases of adult administration included 19 with therapeutic intent, 34 with unknown intent and 26 with non-therapeutic intent (Table). In the cases judged to be 'therapeutic intent' or 'unknown intent', several factors appeared to contribute to the administration of an overdosage: administration of two medicines containing the same ingredients, failure to use a measuring device, use of an adult product, use of the wrong product due to product misidentification, and two or more caregivers administering the same medication. In the cases of non-therapeutic intent, circumstances involved attempts at sedation and several included apparent attempts of overt child-abuse and were under investigation by law enforcement authorities.

Table. Contributing factors to fatalities associated with adult administration of a cough and cold medication to a child

	Expert Panel Assessment of Intent		
	Non-therapeutic intent (n=26)	Therapeutic intent (n=19)	Unable to determine intent (n=34)
Combination product	6	14	13
More than 1 product with same ingredient	1	5	1
Product intended for adults administered to child	2	0	1
Site was daycare or babysitter home	10	1	0
Incorrect or no measuring device used	3	3	0
Attempting to sedate child	6	0	0
Abuse (excludes sedation)	3	0	0
Homicide suspected	10	0	0

Limitations

The primary limitation of our analysis is the use of databases containing spontaneously reported information. It is likely that other cases with some association to cough and cold medications have occurred, but have not been reported. We addressed this concern with extensive attempts to find cases, including sources not always available such as manufacturer's adverse event databases. The true total number of cases is unknown and likely to be higher than reported herein. Like all retrospective analyses, the data in some cases were limited and the accuracy of the information reported cannot be validated. We attempted to compensate for this characteristic by using a expert panel with diverse backgrounds and by including all cases with any suggestion of cough or cold toxicity. Finally, we addressed only deaths related to the nonprescription cough and cold products rather than all adverse events. In the overall risk-benefit evaluation of these products, death informs only a portion of the assessment.

Discussion

Our results provide the most comprehensive evaluation available of pediatric fatalities associated with nonprescription cough and cold medications. Our search strategy discovered many fatalities not previously considered in the evaluation of these medications. The expert panel concluded that 103 cases involved a plausible relationship between a nonprescription cough and cold ingredient and death. In cases where the dosage could be assessed, the panel concluded that evidence of an overdose was present. Deaths following use of cough and cold products in children appear to arise from product misuse rather than adverse effects resulting from recommended doses. There were three scenarios in which deaths occurred: adult administration with therapeutic intent, adult administration with non-therapeutic intent or self-administration by a child.

The age group of children less than 2 years was the most commonly involved. Their small size may facilitate inadvertent administration of an overdose. It is also harder for young children than for older children to communicate emerging adverse effects to their caregiver. A potential contributor to the predominance of young children is the fact that the package label of nonprescription cough and cold medications does not provide dosing information for children less than 2 years of age. Instead, FDA regulation requires the label to instruct the caregiver to call a physician, a difficult and unlikely action for many caregivers in the United States. Based in part on the panel's analysis, cough and cold products for use in children under the age of 2 years were voluntarily withdrawn from the American market by the manufacturers. (30)

In cases judged to involve therapeutic intent, several factors contributed to administration of an overdose: administration of two or more medicines that contained the same ingredients, failure to use a measuring device or use of an inappropriate device, use of a product intended for adults, use of the wrong product due to product misidentification, and two or more caregivers administering medications to the child. Potential solutions include clear, legible labels that explicitly name the ingredients and improved medication administration devices that clearly indicate the appropriate dosage and cannot be separated from the medication. In the past, not all manufacturers provided measuring devices with their products. Furthermore, measuring devices are not standardized across the pharmaceutical industry and the device for each product is different. The possibility of repeated inadvertent administration of an overdose exists. The contributions to medication errors must be more accurately identified and standardized solutions implemented.

The deaths related to non-therapeutic intent is a new and particularly concerning finding. In many cases, the caregiver admitted their intent to sedate the child, a use for which these products are neither labeled nor intended. In other cases, the documentation explicitly stated that the child did not have cold symptoms, indicating a different intent of the caregiver. It is important to understand that

many of the cases where the intent was to produce sedation occurred outside the child's normal bed time. In other words, these were not attempts to facilitate sleep by reducing nighttime distress due to cough and cold symptoms. To minimize deaths that result from similar attempts, nonprescription labels should clearly advise against the use of these products for sedation. Further, educational interventions targeted at healthcare providers, parents, and child care facilities could reduce inappropriate use of these products.

The fatalities involving malicious intent are particularly challenging because it is unlikely that label changes or restriction of access would effectively deter perpetrators. Other inappropriate means of controlling a child's behavior would remain available: adult formulations of the same ingredients contained in children's cough and cold medicines, other medications and chemicals in general, as well as other methods entirely (i.e. physical abuse). Notably, the age, gender and location of death associated with cough and cold medications is similar to cases in the child abuse literature.(31) It is recognized that the extent of fatal child abuse is underestimated.(32) One prudent intervention could be to standardize investigations of pediatric deaths and to routinely include medication screening in these investigations. The concept of child fatality teams was developed to address the recognized inadequacy of current systems in identifying the cause of unexpected death among children. A child fatality team provides a standardized evaluation of each pediatric death.(33) A small contribution from poisoning has been recognized, however, it is clear that many of these cases require blood testing for detection, which many postmortem examinations do not include routinely. After excluding suffocation and sudden infant death syndrome, the Arizona Child Fatality Review Program reported 48 unexpected infant deaths in Arizona in 2006. Ten of 21 infants that had autopsy and toxicology tests performed were positive for cough and cold medications.(34) Postmortem viral diagnostic studies should also be encouraged to identify the role of serious viral infections like respiratory syncytial virus. Children abused with medications likely comprise part of the hidden cases of child abuse. Improved investigation of child deaths would allow more accurate ascertainment of cases and perhaps identify additional risk factors.

The results of Schaefer, et al, (35) regarding adverse events in children complement our results. Using a nationally representative sample of emergency departments in the United States, Schaefer projected from a sample of 301 cases that there were approximately 7091 pediatric visits related to cough and cold medications in the United States annually. The study included all adverse events and does not report severity of the event. The predominant age group affected was 2 to 6 years of age. Our study found that most reported deaths involved children under the age of 2 years. Many of the reasons for an adverse event reported by Schaefer were similar to ours (excess dose administered, wrong medication given, etc.) with the important exception that attempts to harm the child or sedate the child were not noted. Some deaths may have been routed directly to a medical examiner's office. Furthermore, deaths after use of a cough

and cold product are likely rare and their sample size may have been too small to capture outcomes such as death.

The nonprescription cough and cold medications offer an important opportunity for public health intervention. The relatively small number of deaths over several decades is somewhat reassuring given their common use. However, these products are intended for symptomatic relief; therefore, the risk of harm must be reduced as much as possible. An earlier US FDA advisory committee concluded in 1972 that cough and cold medications were effective. This conclusion was reached using the concept of extrapolation of data obtained in adult studies to children.(36) This method has been challenged and is still a matter of debate. The most recent advisory committee concluded in 2007 that cough and cold medications lack evidence of efficacy. Additional research addressing both the appropriateness of extrapolating data from adult studies to children and evaluating efficacy in children with better methodology reportedly is planned.

Many of the factors related to inadvertent overdose identified by the expert panel are preventable and interventions could potentially reduce the deaths associated with cough and cold products substantially. A successful public health intervention requires clear identification of contributing factors, implementation of effective tools to address each factor, and ongoing active surveillance to document the effect of interventions and to detect new developments.

Nota bene:

A draft of this analysis was also presented by RMPDC at the FDA advisory committee meeting on October 18-19, 2007 *(see **Attachment 1**)*. Differences in the figures between the 2007 presentation of the draft data and the final report are shown and explained in ***Attachment 2.***

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Attachment 1

Safety and Efficacy of Over-the-Counter (OTC) Cough and Cold Medicines for Pediatric Use

Joint Meeting Between the Nonprescription Drugs & Pediatric Advisory Committees

October 18-19, 2007

Agenda

Efficacy Research	**Dr. Philip Walson** Cincinnati Children's Hospital
Pharmacokinetics	**Dr. Cathy K. Gelotte** McNeil Consumer Healthcare
Safety	**Dr. Edwin K. Kuffner** McNeil Consumer Healthcare
	Dr. Richard Dart Rocky Mountain Poison and Drug Center, Denver Health Authority, Professor, University of Colorado School of Medicine
Industry Recommendations and Action Plan	**Dr. Linda Suydam** President, CHPA

Review of National Poison Center Data and Fatality Root Cause Analysis

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and Drug Center, Denver Health Authority
Professor, University of Colorado School of Medicine

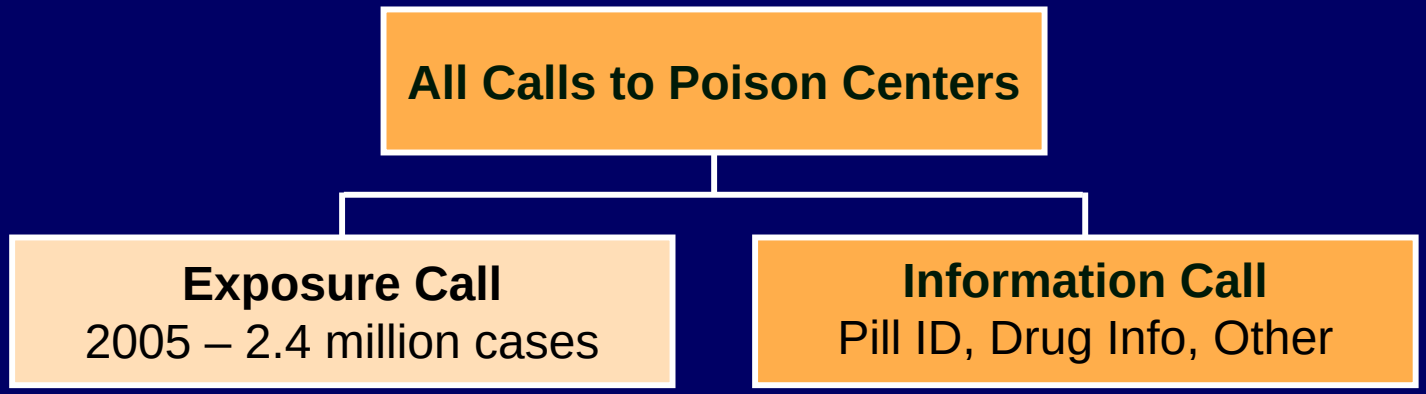
Presentation Outline

- **Maryland Poison Center Data**
- **National Poison Center Data**
- **Consensus Panel Review of Child Fatalities Related to Cough and Cold Ingredients**

U.S. Poison Centers
Valuable Tool to Understand Drug Safety

- **Nationwide network of 61 call centers**
  - **Provide advice on care**
  - **Collect data**
- **Trained, certified professionals take calls**
- **Nationally standardized data collection system**
- **Limitations of data**
  - **Spontaneous reporting**

NPDS
Exposure Does Not Equal Overdose



- **Exposure – Any case in which patient actually took the drug or chemical involved**
  - **May involve therapeutic dose or overdose**
  - **“Outcome – No effect, minimal, moderate, major, death**

Maryland Poison Center, 2004
No Major Effects with Cough/Cold Exposures

- **Total 18,575 exposure to all substances <6 yrs**
  - **Exposure: any case in which patient actually took the drug or chemical involved**
- **1,078 cough/cold exposures <6 yrs**
  - **5 moderate effect cases**
  - **No fatalities or major effects**
  - **1,073 cases (minor or not followed)**

Poison Centers
FDA Therapeutic Dose

	Dose for 10 kg, 24 month old child
Drug	FDA Briefing Book Therapeutic Dose, 2-6 y (mg)
Diphenhydramine	6.25
Pseudoephedrine	15
Dextromethorphan	2.5 – 7.5
Chlorpheniramine	1
Brompheniramine	1
Phenylephrine	2.5

Poison Center Referral Dose

Drug	Dose for 10 kg, 24 month old child	
	FDA Briefing Book Therapeutic Dose, 2-6 y (mg)	Poison Center Referral Dose (mg)
Diphenhydramine	6.25	75
Pseudoephedrine	15	160
Dextromethorphan	2.5 – 7.5	75
Chlorpheniramine	1	14
Brompheniramine	1	20
Phenylephrine	2.5	40

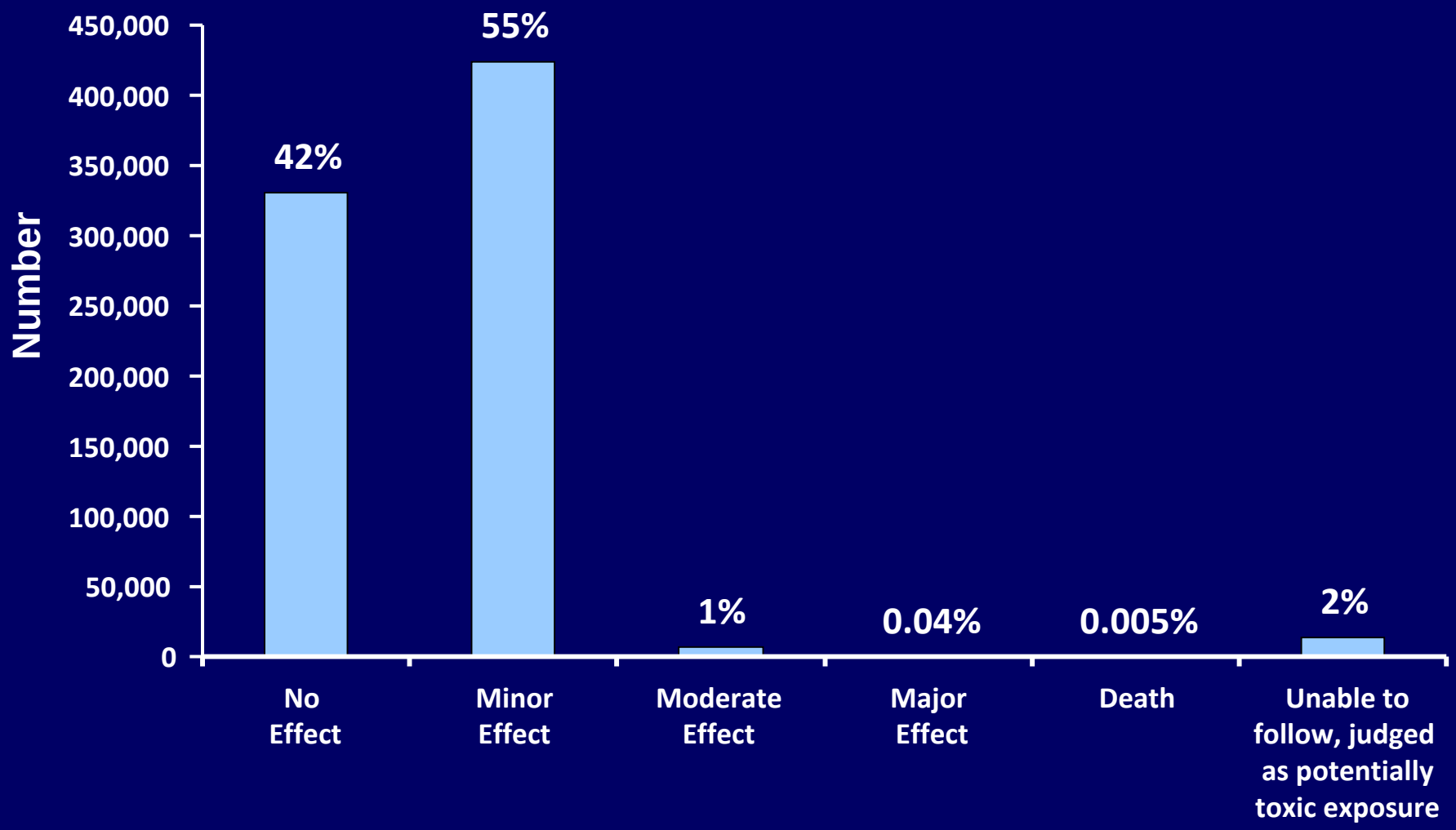
Poison Centers
No Referral Until 10-30 Times Therapeutic Dose

	Dose for 10 kg, 24 month old child		Ratio
Drug	FDA Briefing Book Therapeutic Dose, 2-6 y (mg)	Poison Center Referral Dose (mg)	Referral/ Therapeutic
Diphenhydramine	6.25	75	12
Pseudoephedrine	15	160	11
Dextromethorphan	2.5 – 7.5	75	10 – 30
Chlorpheniramine	1	14	14
Brompheniramine	1	20	20
Phenylephrine	2.5	40	15

AAPCC National Poison Data System (NPDS) Analysis

- **Goal – Identify cases and characterize the exposure**
- **Methods**
  - **Human exposure age <12 years**
  - **Exposure to one of 26 cough and cold ingredients**
  - **Period January 1, 2000 – June 30, 2007**
  - **NPDS searched by AAPCC**
    - **A total of 774,960 exposures reported over 6.5 yrs**

NPDS
97% Minor or No Effect



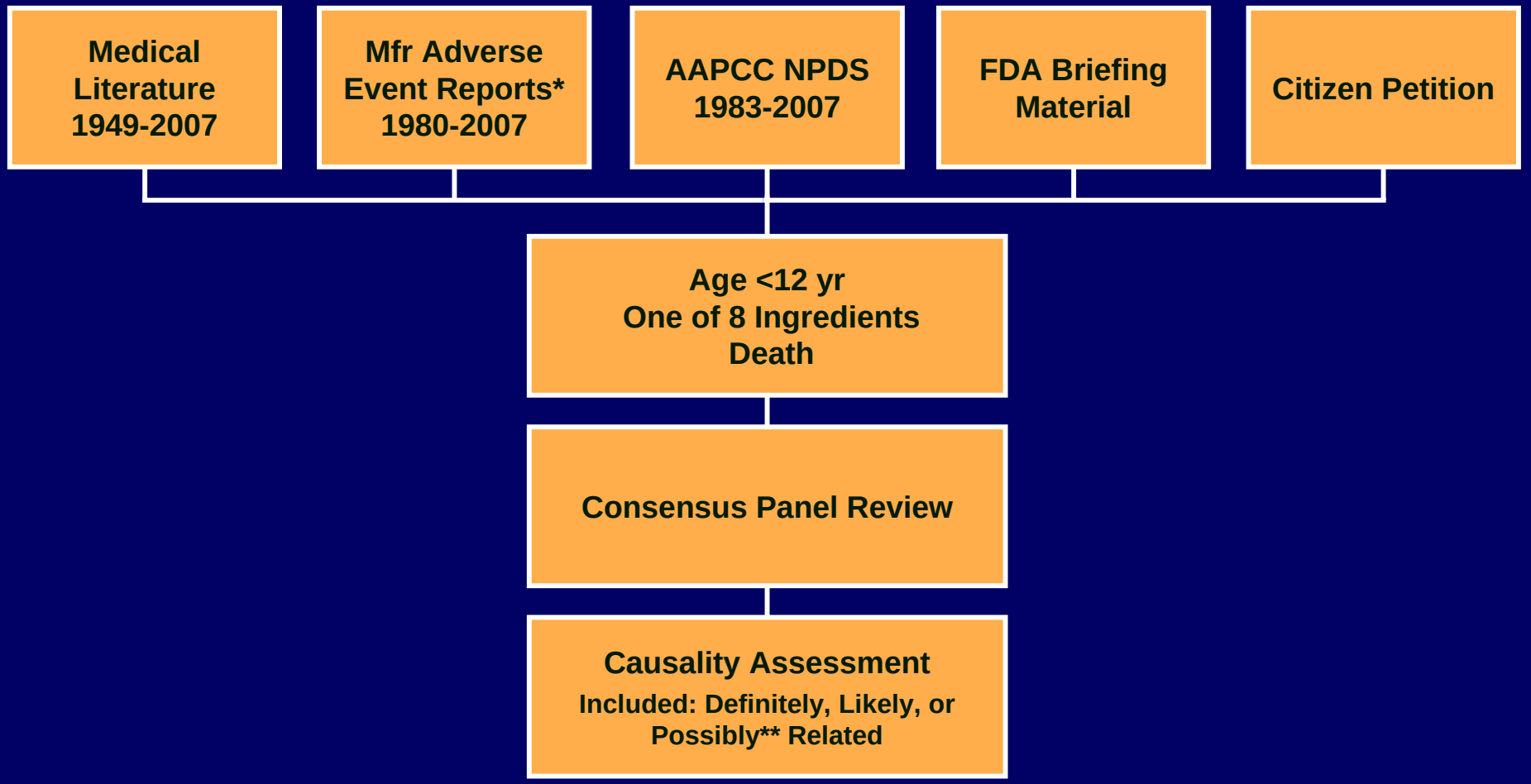
Consensus Panel Analysis of Reports

- **Assess relationship between cough and cold medicine and death**
- **Categorize dosage**
  - **Therapeutic dosage, supratherapeutic dosage**
  - **Unable to determine**
- **Describe apparent root cause of death**

Consensus Panel Members Independent and Diverse

Name	Expertise
William Banner, MD, PhD	Pediatrics, Critical Care
G. Randall Bond, MD	Pediatrics, Toxicology
Ralph Kaufmann, MD	Pediatrics
Tony Manoguerra, PharmD, ABAT	Pharmacy, Toxicology
Robert Palmer, PhD, ABAT	Forensic Toxicology
Ian Paul, MD	Pediatrics
Barry Rumack, MD	Pediatrics, Toxicology
David Winston, MD, PhD	Forensic Medicine

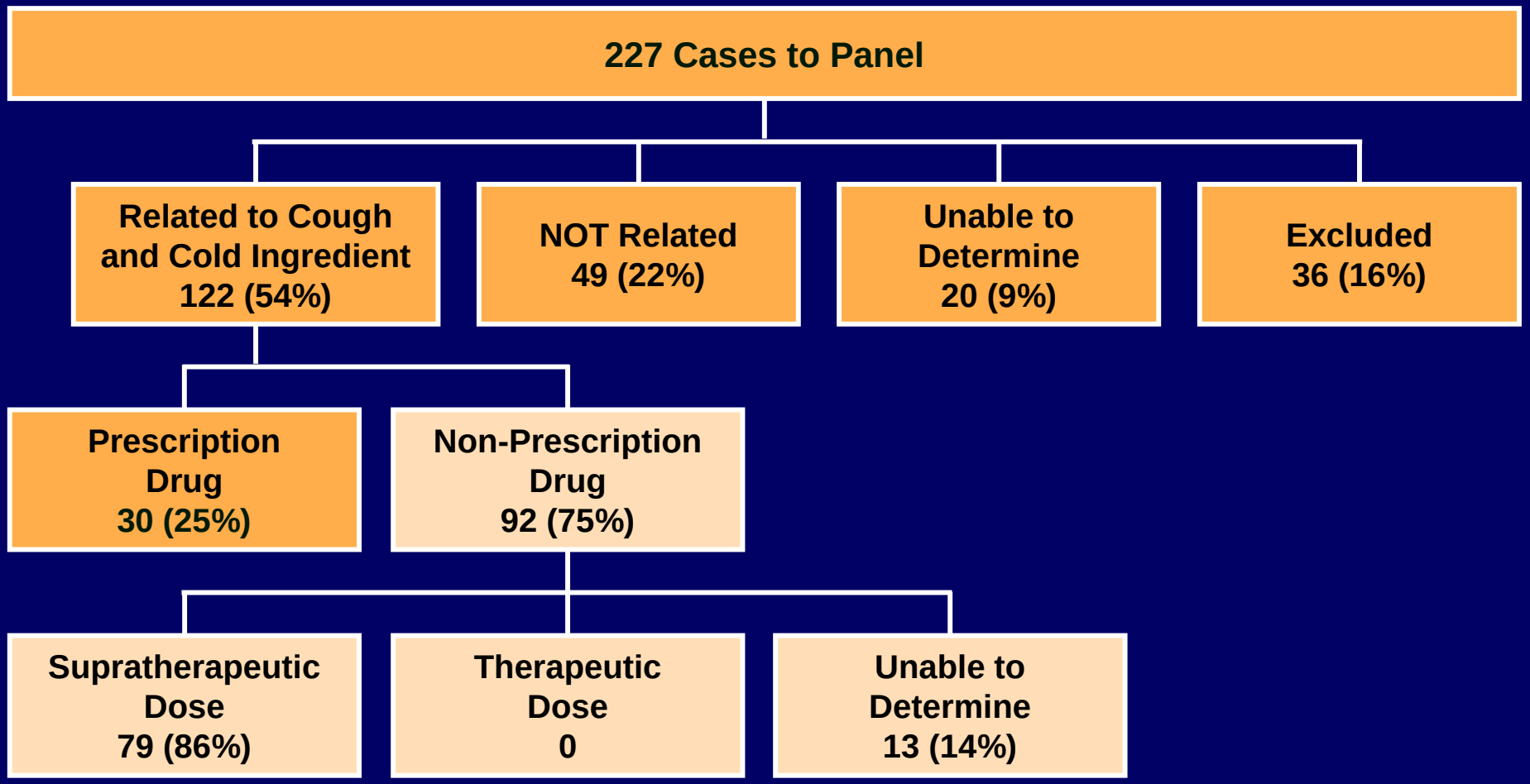
Consensus Panel Analysis
Comprehensive Scientific Review



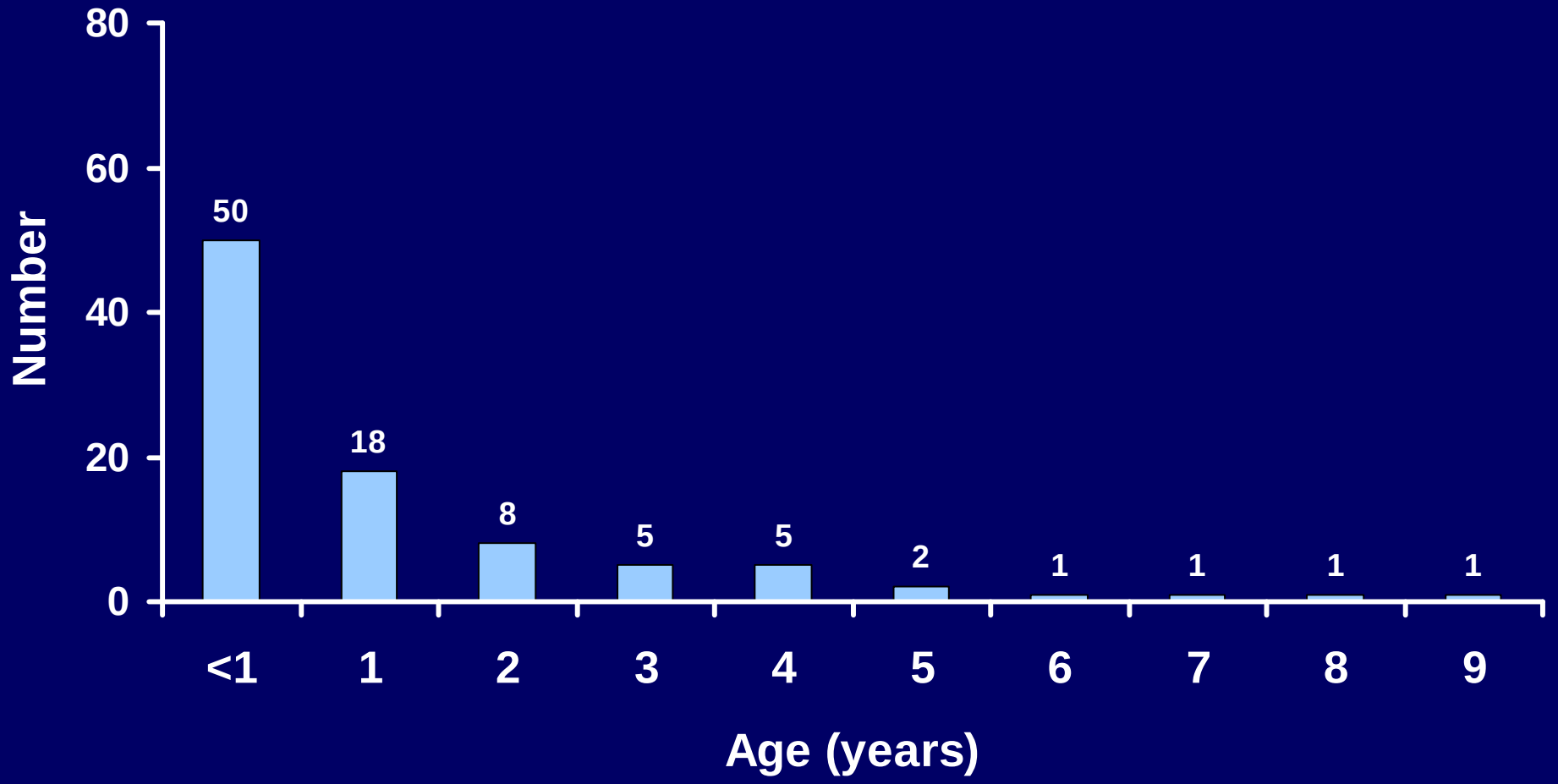
*Includes databases from many manufacturers, including reports from the CHPA Safety presentation

**History and/or drug level may be consistent with exposure, clinical course known or unknown, other cause of death possible

Consensus Panel Results



Consensus Panel Age Distribution
74% Children <2 yrs



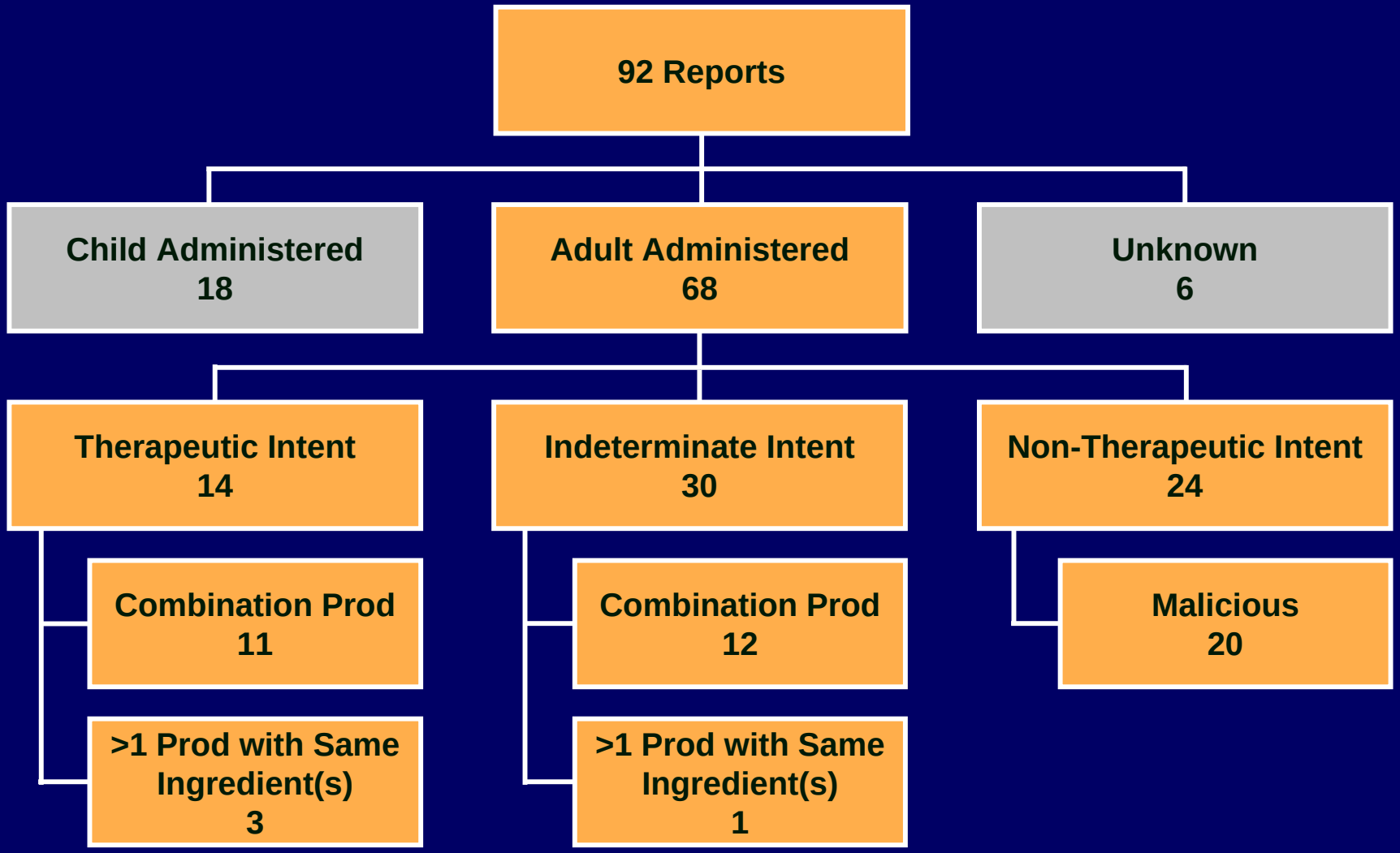
Consensus Panel Administration Occurs Without Symptoms

	Total (excluding Unable to Determine) N=43
Cough and cold symptom explicitly denied	**24 (44%)**

Consensus Panel
Most Events Occur in the Home

	<2 yrs n	2 to <6 yrs n	6 to <12 yrs n
Home	**24**	**12**	**3**
Daycare/baby-sitter	**12**	**0**	**0**
Hospital	**1**	**0**	**0**
Unknown site (n)	**32**	**8**	**1**

Consensus Panel
Supratherapeutic Use Related to Death



Attachment 2

Summary of differences between the RMPDC presentation of the draft data at the FDA advisory meeting on October 18-19, 2007, and the final report

	Presentation of Draft Data October 2007	Final Report	Reason for Difference
Cases reviewed by panel	227	189	October 2007 presentation combined all excluded cases (n=36) whether they were excluded prior to or during panel review. This analysis included foreign reports. Final Report analysis distinguished between cases that did not meet inclusion criteria (n=38; 25 did not include index drug + 13 foreign reports) and those that were excluded during panel review (n=11; 10 duplicates, 1 in utero exposure).
Cases meeting inclusion criteria	191 evaluated (227 reported minus 36 excluded)	178 evaluated (189 reported minus 11 excluded by panel)	Difference due to exclusion of 13 foreign cases in the current report
Related to cold med.	122	118	Difference resulting from exclusion of 13 foreign cases in the current report
Not related to cold med.	49	41	
Unable to determine rel.	20	19	
Nonprescription cold medicine (nonRX)	92	103 (82 nonRX only + 21 nonRX and RX)	October 2007 presentation put cases with nonRX+RX exposures in RX box; current report includes these cases in nonRX to be most inclusive
- Supratherapeutic Dose	*79*	*88*	*Current report includes nonRX+RX cases*
- Therapeutic Dose	*0*	*0*	
- Unknown Dose	*13*	*15*	

Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Module 2 - Section #4

Pediatric Safety Data From Clinical Studies on OTC Cough and Cold Medicines

The Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

TABLE OF CONTENTS

1 PEDIATRIC SAFETY DATA FROM CLINICAL STUDIES ON OTC COUGH AND COLD MEDICINES

1.1 Introduction

In the August 16, 2007, *Federal Register,* FDA announced a joint meeting (October 18-19, 2007) of the Nonprescription Drugs Advisory Committee (NDAC) and Pediatric Advisory Committee (PAC) to discuss the safety and efficacy of over-the-counter (OTC) cough and cold medicines marketed for pediatric use. The meeting was called in response to a citizen petition submitted to FDA in March 2007 that raised concerns about the safety and efficacy of OTC cough and cold medicines used in children less than six years of age.

The Consumer Healthcare Products Association (CHPA) submitted a briefing book for the committee in advance of the October 2007 NDAC/PAC meeting. Appendix 5 of the briefing book contained Table 5.9, Safety data from prospective clinical trials in children – company sponsored, published literature and post marketing studies.

The sections that follow provide additional information related to published and unpublished clinical studies of pediatric safety of OTC cough and cold medications. Section 1.2 outlines the published studies included in Table 5.9 of Appendix 5 in the CHPA briefing book and provides tabular summaries of six relevant published studies not included in Table 5.9, but reviewed after preparation of the briefing book. Section 1.3 provides an outline of the unpublished studies included in Table 5.9 of Appendix 5 in the CHPA briefing book and a tabular summary of one unpublished study that was not included in Table 5.9, but reviewed after preparation of the briefing book.

In summary, pediatric safety data are available from 23 published studies and 11 unpublished studies. These data support the safety of the use of OTC cough and cold medications in children.

1.2 Published Studies with Pediatric Safety Data on OTC Cough and Cold Medicines

Table 5.9 in Appendix 5 of CHPA's briefing book for the October 2007 NDAC/PAC meeting included 22 individual studies that had been reported in 25 published articles. Recent additional review of the 22 individual studies indicated that five of the 22 studies did not provide pediatric safety information relevant to the use of OTC cough and cold ingredients. Table 1 of this document provides a list of these five studies and includes an abbreviated citation and the reason the studies were considered not relevant.

Table 1. Listing of Five Studies Included in Table 5.9 of Appendix 5 of the October 2007 CHPA Briefing Book That Did Not Provide Pediatric Safety Information Relevant to the Use of OTC Cough and Cold Ingredients

No.	Abbreviated Article Citation	Reason Not Relevant
1.	Merenstein D et al. Arch Pediatr Adolesc Med 2006;160;707-712.	Evaluated children with frequent night-time awakenings
2.	Porta M et al. Ann Allergy 1986;57:340-342.	Not a trial, reported on an epidemiological study of prescriptions filled and subsequent hospitalizations
3.	Reece C et al. Am J Dis Child 1966;112;124-128.	Efficacy results reported but no safety results
4.	Wezorek C et al. Clin Toxicol 1995;33:554.	Not a trial; reported on a series of accidental ingestions
5.	Jaffe G et al. Cur Med Res Opin 1983;8:594-599.	Evaluated only cough and cold products that contained codeine (not OTC cough and cold medications)

Thus, Table 5.9 in Appendix 5 of CHPA's briefing book for the October 2007 NDAC/PAC meeting contained relevant pediatric safety data for 17 individual studies reported in 20 published articles. Table 2 provides a list of the 17 published studies and includes an abbreviated citation.

Table 2. Listing of 17 Relevant Published Studies Included in Table 5.9 of Appendix 5 to the October 2007 CHPA Briefing Book

No.	Abbreviated Article Citation
1.	McGovern et al. J Ann Allergy 1959;17:915-922.
2.	Lipschultz A. Ann Allergy 1960;18:998-1003.
3.	Carter C. Am J Med Sci 1963;245:713-717.
4.	Todd G et al. Curr Med Res Opin 1975;3:126-131.
5.	Simons et al. E J Allergy Clin Immunol 1982;69:376-381.
6.	Weippl G et al. Pharmatherapeutica1983;3:405-409.
7.	Weippl G. Clin Ther 1984;6:475-482.
8.	Sakchainanont et al. B J Med Assoc Thai 1990;73;96-101.
9.	Hutton N et al. J Pediatr1991;118:125-130.
10.	Korppi M et al. Acta Paediat Scand 1991;80:969-971.
11.	Taylor J et al. J Pediatr 1993;122:799-802.
12.	Martinez-Gallardo F et al. Proc West Pharmacol Soc 1994;37:157-158.
13.	Simons F et al. J Pediatr 1996;129:729-734.
	Gu X et al. J Allergy Clin Immunol 1996;97:199.
14.	Tinkleman D et al. Pediatr Asthma Allergy Immunol 1996;10:9-17.
15.	Serra H et al. Br J Clin Pharmacol 1998;45:147-150.
16.	Jayaram S et al. J Indian Med Assoc 2000;98:68-70.
17.	Paul I et al. Pediatrics 2004;114:e85-e90.
	Paul I et al. Clin Ther 2004;26:1508-1514.
	Yoder K et al. Clin Pediatr 2006;45:633-640.

Since preparation of the October 2007 briefing book, six additional studies have been identified. Tabular summaries of these six additional published studies are provided in Table 3. These six studies were not included in the CHPA briefing book previously submitted to the FDA in advance of the October 2007 meeting. These six relevant studies were of cough and cold products, included children less than 12 years of age, and were studies of single-ingredient or combination-ingredient products that included pseudoephedrine, diphenhydramine, chlorpheniramine, and/or brompheniramine.

Four of these six studies were of an acute condition, ie, upper respiratory tract infection, seasonal allergic rhinitis, hay fever, or seasonal allergic rhinoconjunctivitis, and enrolled children less than 12 years of age [1,2,3,4]. Two of these studies also included adolescents; Shanon [3] included children eight to 16 years of age and Villa Asensi [4] included children six to 16 years of age. The remaining two studies evaluated children with whooping cough [5] and serous otitis media [6].

In summary, relevant pediatric safety data are available from 17 published studies listed in Table 5.9 of Appendix 5 of the CHPA briefing book for the October 2007 NDAC/PAC

meeting and six additional studies summarized in this section. These 23 published studies provide support for the safety of use of OTC cough and cold medications in children.

Table 3. Summaries of Six Relevant Additional Published Studies Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
Boner AL et al. Allergy 1989;44:437-441. [1]	R AC SB	Loratadine 5 mg qd	Susp Oral	21 (21)	7.6 y 14M, 7F	**Study Population:** Children with moderate to severe seasonal allergic rhinitis.
		Dexchlorphenir-amine 1 mg q8h 14 days	Syrup Oral	19 (19)	7.8 y 12M, 7F	**Efficacy:** Severity of symptoms based on investigator and child/parent total symptom score (nasal discharge, stuffiness, itching and sneezing, itching or burning eyes, watery eyes, redness of eyes, itching of ear or palate) significantly ($p<0.01$) improved with both drugs during the 14 days. Rhinoscopy showed no significant differences between the two drugs with both significantly reducing nasal secretion and nasal stuffiness.
				Overall: 40	Overall: 7.7 y (4-12 y) 26M, 14F	
						Safety: One loratadine-treated subject discontinued on day 7 due to nausea, vomiting, and lipothymia. Adverse events included: somnolence (dexCPM-4), epistaxis (dexCPM-2, loratadine-2). Hematological counts, electrolyte balance, liver and kidney function did not show any toxic effects with either drug.
						Comments: Children <6 y and those weighing <20 kg received half of the dose.

Table 3. Summaries of Six Relevant Additional Published Studies Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
Clemens CJ et al. J Pediatr 1997;130:463-466. [2]	R DB PC MC	Brompheniramine maleate 2 mg/5 ml + phenylpropanolamine HCl 12.5 mg/5 ml	Solution Oral	28 (28)	23.7 months 15M, 13F	**Study Population:** Children 6 months through 5 y with an upper respiratory tract infection of less than 7 days duration. **Efficacy:** Percent of children with the following symptoms 2 h after each dose: runny nose (Bpm+Ppm-50.6, Pbo-57.5; p=NS), nasal congestion (Bpm+Ppm-48.8, Pbo-50.6; p=NS), cough (Bpm+Ppm-49.0, Pbo-43.1; p=NS).
		Placebo	Solution Oral	31 (31)	30.1 months 13M, 18F	
		48 hours		Overall: 59	Overall: 28M, 31F	**Safety:** Percent of children asleep 2 h after each dose: Bpm+Ppm-46.6, Pbo-26.5; p=0.01. No other safety data were reported. **Comments:** Children 6 months-2 y received a half-teaspoon; children 2-5 y received 1 teaspoon, no more than every 4 h. Parents were instructed to give the medication whenever they thought it was necessary.

Table 3. Summaries of Six Relevant Additional Published Studies Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
Shanon A et al. Dev. Pharmacol Ther 1993;20:239-246. [3]	R DB CO	Chlorpheniramine 2 mg qid (8-12 y) or 4 mg qid (13-16 y) Astemizole 5 mg qd (8-12 y) or 10 mg (13-16 y) 3 weeks	Capsule Oral Capsule Oral	Overall: NA (103)	Overall: 64M, 39F	**Study Population:** Children 8 to 16 y of age with isolated allergic rhinitis or hay fever. **Efficacy:** Both Chlorpheniramine and Astemizole showed no significant effects on the visual retention test and the continuous performance test. On the visual aural digit span test, Astemizole-treated subjects scored higher than at baseline, suggesting that a practice effect was present. **Safety:** Number of subjects discontinuing due to AEs: Chlorpheniramine-2 (drowsiness), Astemizole-3 (headaches, 'stomach flu', or short attention span and feeling moody). No clinical or statistically significant differences in AEs between the two drugs or between each drug and baseline were observed; in particular no differences were noted for tired, dizzy, hungry, or nervous. Other AEs reported included abdominal pain (8), vomiting (6), nose bleed (2), restlessness (2), irritability (2), diarrhea (2), constipation (1), and stiff neck (1).

Table 3. Summaries of Six Relevant Additional Published Studies Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
Villa Asensi JR et al. Acta Ped Espanol 1988;46:113 -116. [4]	R PC	Chlorpheniramine	NA			**Study Population:** Children with seasonal allergic rhinoconjunctivitis.
		Terfenadine	NA			**Efficacy:** Total improvement from baseline for seven symptoms (nasal congestion, rhinorrhea, itching nose, itching throat, itching eyes, watery eyes, and red eyes) was significant with Cpm, Ter, and Ast ($p<0.01$) and also with Pbo ($p<0.05$); Ast was significantly superior to Pbo ($p<0.05$). Ast was significantly ($p<0.05$) superior to Ter and Cpm in the relief of itching eyes. Only Ast was significantly ($p<0.05$) superior to Pbo in the improvement of red eyes. No significant difference was observed between the Cpm, Ter, and Ast vs Pbo for nasal congestion. Ast and Ter significantly ($p<0.05$) improved rhinorrhea.
		Astemizole	NA			
		Placebo	NA			
		7 days		Overall: NA (65)	Overall: (6-16 y)	**Safety:** Side effects were minor and infrequent in all treatment groups and similar to the Pbo group.

Table 3. Summaries of Six Relevant Additional Published Studies Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
Danzon A et al. Acta Paediatr Scand 1988;77:614 -615. [5]	R DB PC	Diphenhydramine 5 mg/kg/day in three divided doses	Syrup Oral	25 (25)	NA	**Study Population:** Children <12 months of age with characteristic whooping/coughing spells that were not treated with steroids. **Efficacy:** Mean number of coughing fits per day between the 25th and 48th hour after treatment initiation: DPH-22.6, Pbo-20.7; p=NS. No significant difference between diphenhydramine and placebo were observed after adjustment for confounders (number of fits in the previous 24 hours and subject's age). **Safety:** Most subjects were monitored for side effects for more than a week. None could be attributed to the active drug or the excipient. Nurses did note that giving the syrup orally resulted in cough paroxysms in 4 (16%) diphenhydramine-treated children and 2 (8.3%) placebo-treated children.
		Placebo	Syrup Oral	24 (24) Overall: 49	NA	

Table 3. Summaries of Six Relevant Additional Published Studies Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Citation	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
O'Shea JS et al. Ann Otol Rhinol Laryngol Suppl 1980;89:285 -289. [6]	DB PC	Diphenhydramine 5 mg/kg/day+ Pseudoephedrine 5 mg/kg/day in 3 divided doses	Oral	27 (NA)	NA	**Study Population:** Children age 3 to 9 y diagnosed within one month before entry with the first known episode of serous otitis media. **Efficacy:** No differences were noted between Dph+Pse and placebo for improvements in hearing (as reported by the parents and assessed audiometrically), changes in tympanometry, and percent of subjects that still had a hearing loss of 20 or more decibels 3 months after study entry. Percent of children improved for symptoms not directly related to hearing ability (especially upper respiratory congestion) during the study: Dph+Pse-81, Pbo-42; p<0.01. **Safety:** Percent of children developing drowsiness: Dph+Pse-37, Pbo-4; p<0.05. Other AEs included increased activity at home and school (Dph+Pse-2, Pbo-2) and nighttime cough (Pbo-1). **Comments:** Children had appointments at 4-week intervals for 12 weeks. Children were advised to stop taking the medication if no visible fluid was observed in either middle ear, no hearing loss was detected in both ears, and a normal tympanogram was obtained.
		Placebo	Oral	28 (NA)	NA	
		3 months		Overall: 55 (61)	Overall: 6 y 33M,22F	

Abbreviations: AC=active controlled, AE=adverse event, Ast=astemizole, Bpm=bromopheniramine, CO=crossover, Cpm=chlorpheniramine, DB=double-blind, dexCPM=dexchlorpheniramine, Dph=diphenhydramine, F=female, HCl=hydrochloride, M=male, MC=multicenter, NA=not available, NS=not significant, Pbo=placebo, PC=placebo-controlled, Ppm=phenylpropanolamine, Pse=pseudoephedrine, qd=once daily, qid=four times daily, q8h=every 8 hours, R=randomized, SB=single-blind, susp=suspension, Ter=terfenadine.

1.3 Unpublished Studies with Pediatric Safety Data on OTC Cough and Cold Medicines

Table 5.9 in Appendix 5 of CHPA's briefing book for the October 2007 NDAC/PAC meeting included 11 unpublished studies. Recent additional review of the 11 studies indicated that one study did not provide pediatric safety information relevant to the use of OTC cough and cold ingredients. Table 4 lists information for the one study including an abbreviated citation and the reason the study was considered not relevant.

Table 4. Listing of One Study Included in Table 5.9 of Appendix 5 of the October 2007 CHPA Briefing Book That Did Not Provide Safety Information Relevant to the Use of OTC Cough and Cold Ingredients

Abbreviated Report Citation	Reason Not Relevant
McNeil Study 00-131, Report Number CSR-272.	Evaluated children with primary nocturnal enuresis

Thus, Table 5.9 in Appendix 5 of CHPA's briefing book contained relevant pediatric safety data for ten unpublished studies. Table 5 provides a list of the ten unpublished studies.

Table 5. Listing of 10 Relevant Unpublished Studies Included in Table 5.9 of Appendix 5 to the October 2007 CHPA Briefing Book

No.	Abbreviated Report Citation
1.	McNeil Statistical Report (T&A) #10 (000107)
2.	McNeil Statistical Report (T&A) #13 (000113)
3.	McNeil Statistical Report (T&A) #15 (000117)
4.	McNeil Study 97-024
5.	McNeil Study 99-086
6.	Wyeth Study AQ-99-02
7.	Wyeth Study AQ-99-03
8.	Wyeth Study AQ-00-04
9.	Wyeth Study AR0003
10.	Wyeth Study AR0004

One additional unpublished study has been identified since preparation of Table 5.9 of the October 2007 CHPA briefing book. Table 6 provides a tabular summary for that study.

In summary, relevant pediatric safety data are available from ten unpublished studies listed in Table 5.9 of Appendix 5 of the CHPA briefing book for the October 2007 NDAC/PAC meeting and one additional study summarized in this section. These 11 unpublished studies provide support for the safety of the use of OTC cough and cold medications in children.

Table 6. Summary of One Relevant Additional Unpublished Study Identified and Summarized After Preparation of the CHPA Briefing Book, October 2007

Study Report Date (Report Number)	Study Design	Medication Dose Duration	Dosage Form Route	N Efficacy (Safety)	Mean Age (Range) Gender	Study Results
November 1978 (Statistical Report (T&A) #5) (000097) [7]	Multi-center, Open-label	APAP 325 mg+ Pseudoephedrine Hydrochloride 30 mg+Chlor-pheniramine Maleate 2 mg [a] up to 4 days Multidose	Tablet oral	92	33.76 y (9 y-86 y)	**Study Population:** Subjects at least 6 y old with symptoms of upper respiratory infection or allergic rhinitis. **Efficacy:** As assessed by the investigators, 79% of subjects achieved good or excellent results. 16 symptoms were rated pre- and post-medication use on a 4-point scale as none (0), mild (1), moderate (2), and severe (3). Post-medication symptom severity levels were significantly lower than pre-medication levels, all p-values < 0.000007. Each of the 16 symptoms showed an average improvement in severity level of between 62% and 94%, for an overall average improvement of 78%. **Safety:** 18 (20%) subjects reported AEs. Reported AEs included (number of AEs): drowsy (6), dry mouth (3), dizzy (2), insomnia (2), nervousness (1), slight jittery feeling (1), dryness of eyes and throat (1), nosebleed (1), chills (1), weakness (1), sleepy (1), severe headache (1), diarrhea (1), nausea/epigastric distress (1). **Comments:** Subjects were both children and adults. Subjects were instructed to take study medication for a period of up to 4 days or until complete recovery, whichever came first. a: Adults (12 y or older) were instructed to take 2 tablets three or four times daily. Children (6 to < 12 y) were instructed to take one tablet three or four times daily.

1.4 Summary

In summary, pediatric safety data are available from 23 published studies and 11 unpublished studies. These data support the safety of the use of OTC cough and cold medications in children.

1.5 References

1. Boner AL, Miglioranzi P, Richelli C, et al. Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. Allergy 1989;44:437-441.
2. Clemens CJ, Taylor JA, Almquist JR, et al. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? J Pediatr 1997;130:463-466.
3. Shanon A, Feldman W, Leikin L, et al. Comparison of CNS adverse effects between astemizole and chlorpheniramine in children: A randomized, double-blind study. Dev. Pharmacol Ther 1993;20:239-246.
4. Villa Asensi JR, Garcia-Hernandez G, Nunez de Prado C, et al. Estudio comparativo de los antihistaminicos Astemizol, Terfenadina y Clorfeniramina en el tratamiento sintomatico de la rinoconjuntivitis alergica estacional en la infancia. Acta Ped Espanol 1988;46:113-116.
5. Danzon A, Lacroix J, Infante-Rivard C, et al. A double-blind clinical trial on diphenhydramine in pertussis. Acta Paediatr Scand 1988;77:614-615.
6. O'Shea JS, Langenbrunner DJ, McCloskey DE et al. Diagnostic and therapeutic studies in childhood serous otitis media: Results of treatment with an antihistamine-adrenergic combination. Ann Otol Rhinol Laryngol Suppl 1980;89:285-289.
7 . McNeil Consumer Products Company Statistical Report #5 (000097): Phase IV Efficacy and Safety Study of Reformulated CoTylenol Tablets. Fort Washington, PA: November 1978. (Data on file)

Docket FDA-2008-N-0466

Part 15 Hearing on

Over-the-Counter Cough and Cold Medications for Pediatric Use

Written Response to FDA Questions

Module 3 of 3

Educational Program on Oral Pediatric Cough and Cold Medicines

Pediatric Task Force of the Consumer Healthcare Products Association

December 2, 2008

Educational Program on Oral Pediatric Cough and Cold Medicines

Overview

The CHPA educational program on pediatric oral pediatric cough and cold medicines has been developed to address the root causes of adverse events with these medicines in children: misuse leading to overdose and accidental ingestion. Initial messaging was focus-tested and refined. A baseline survey of primary caregivers assessing comprehension and conduct was conducted in May 2008; follow-up surveys will be fielded every six months. In addition, the educational program is meant to complement other programs, such as enhancements to child-resistant packaging and the inclusion of dosing instruments with all liquid products. The educational program also runs alongside the scientific program described elsewhere in this submission.

The educational program's primary audiences are parents and other caregivers, as well as their chief influencers: healthcare professionals. CHPA has assembled a steering committee of representatives from a number of different disciplines and constituencies: the American Academy of Family Physicians, the American Pharmacists Association, the National Alliance for Hispanic Health, NACDS Foundation, and the National Consumers League. Other organizations, such as the National Association of Child Care Professionals, also have expressed an interest to help communicate important safe dosing and safe storage information.

The campaign—which is housed at the foundation's web site OTCsafety.org—focuses on the importance of safe dosing, safe storage, and seeking a healthcare professional's advice when there are questions. The campaign features the call to action, *Treat with Care*, and is supported by aggressive media relations and the growing OTCsafety.org web site. The *Treat with Care* campaign includes the following components, many available in both English and Spanish:

— Print and online advertising

  - Print: Conducted advertising that will reach over 225 million parents.
  - Online: English-language online ad content is expected to achieve nearly 180 million impressions; Hispanic online ad content is estimated at 33 million impressions.

— Television, radio, and print public service announcements

— Retail brochure for consumers distributed to retailers and pharmacists.

— Comprehensive brochure for consumers distributed through OTCsafety.org and various health professional and consumer organizations.

— Product, such as a tear sheet or other handout, for patients provided to members of AAFP.

— An online CME activity for members of the American Academy of Family Physicians.

— *The Practice Memo*, developed by the NACDS Foundation and distributed to approximately 140,000 pharmacists in 38,000 chain and 17,000 independent pharmacies

— Partnership with WebMD to distribute information to consumers and healthcare professionals

- Through four major pushes, WebMD is providing both sponsored and collaborative content to over 500,000 healthcare professional subscribers as well as nearly 750,000 consumer subscribers, as well as general content available online for all audiences.

— CME session on pediatric cough and cold medicines and distribution of materials at APhA annual meeting in early 2008, as well as an article series for and survey of pharmacists with APhA.

— Engagement with stakeholders, including participation in 2008 meetings of such groups as the American Public Health Association, the American Academy of Pediatrics, the National Community Pharmacists Association, AAP annual meeting, NCPA annual meeting, and the National Association for the Education of Young Children. Additional plans are underway to further grow this participation in additional meetings in 2009.

The key messages of the Treat with Care campaign are as follows:

- Always read and follow medicine labels exactly and use the measuring device that comes with the medicine.
- Do not give a medicine only intended for adults to your child.
- Only give the medicine that treats your child's specific symptoms.
- Never give two medicines at the same time that contain the same active ingredient.
- Do not use oral cough and cold medicines for children under age 4.
- Never use an OTC medicine to sedate or make your child sleepy.
- Never give aspirin-containing products to your child for cold or flu symptoms unless told to do so by a doctor.
- If your child develops any side effects or reactions that concern you, stop giving the OTC medicine and contact a doctor immediately.
- Keep all medicines out of your child's reach and sight.
- Talk to a doctor, pharmacist, or other healthcare provider if you have any questions.

The fundamental goal of reducing misuse and accidental ingestion rests on increasing parental awareness to safe use and safe storage rules. To this end, CHPA has a survey mechanism in place to help assess the effectiveness of the campaign's messaging and methods. The first survey was fielded in May 2008 by Nielsen. While the survey reinforced a number of consumer behaviors already known—such as a high level of reliance on pediatric oral cough and cold medicines, a high degree of label reading, and the desire among caregivers to select appropriate medicines according to a child's symptoms—the survey also found some areas that confirm the need to pursue the *Treat with Care* Campaign. Among its findings:

- 52 percent of caregivers report using OTC medicines in children under the age of two.

- 64 percent of all caregivers are aware of potential negative side effects of OTC oral cough and cold medicines.

- 16 percent of caregivers gave two or more medicines on their most recent care giving occasion.

Surveys will be fielded biannually.

Educational Program on Oral Pediatric Cough and Cold Medicines

Samples of Educational Materials:

- Public Service Announcements (English/Spanish)
- Consumer Brochures

AS PARENTS, WE'RE IN CHARGE OF OUR KIDS' HEALTH

We can never be too careful when caring for our kids with oral over-the-counter cough and cold medicines.

As a busy mother of three, I have enough to worry about. That's why I always follow these simple rules when giving my kids OTC cough and cold medicines.

- Always follow the label and use the measuring device that comes with the medicine.
- Always safely store medications – out of the reach and out of sight of children.
- Do not use OTC medicines to make your child sleepy.
- Follow new recommendations to not give oral over-the-counter cough and cold medicines to children under the age of 4.
- Talk to your doctor if you have any questions.

OTCsafety.org

TO LEARN MORE ABOUT KEEPING YOUR FAMILY HEALTHY, VISIT OTCSAFETY.ORG.

COMO PADRES, ESTAMOS A CARGO DE LA SALUD DE NUESTROS HIJOS

Nunca podemos ser demasiado cuidadosos a la hora de tratar a nuestros hijos con medicamentos de venta sin receta, de administración por vía oral, para la tos y el resfriado.

Como una madre ocupada y con 3 hijos, tengo suficientes preocupaciones. Es por ello que siempre sigo estas sencillas reglas cuando les doy a mis hijos medicamentos de venta sin receta para la tos y el resfriado.

- Siga siempre las indicaciones de la etiqueta y utilice el dispositivo medidor que viene con el medicamento.
- Siempre almacene los medicamentos de forma segura, fuera del alcance y de la vista de los niños.
- No use medicamentos de venta sin receta para hacer que su hijo tenga sueño.
- Siga las nuevas recomendaciones de no dar medicamentos de venta sin receta, de administración por vía oral, para la tos y el resfriado a niños menores de 4 años.
- Hable con su médico si tiene alguna pregunta.

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PARA MÁS INFORMACIÓN SOBRE CÓMO MANTENER LA SALUD DE SU FAMILIA, VISITE OTCSAFETY.ORG.

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Facts about Children's Cough and Cold Medicines

En el reverso encontrará el texto en español.

Are children's oral OTC cough and cold medicines safe?

Yes. Children's OTC oral cough and cold medicines are safe and effective when given as directed. Although problems with these medicines are very rare and mostly related to incorrect dosing and curious, young children getting into medicines, manufacturers are voluntarily changing labels for children under age 4. Adult cough and cold medicines are not part of this label update.

Will these still be available for use in children?

Yes, these OTC oral pediatric cough and cold medicines are still available to help relieve children's cough and cold symptoms. While new labels will start appearing on these medicines during the 2008-2009 cough and cold season, you may continue to give them to your children age 4 and older.

What will the new labels say?

The medications themselves will be the same medicines you've relied on for years when caring for your children, but soon they will have new labels that advise parents and caregivers not to use them for children under age 4. Current dosing instructions for children, age 4 and older, will not change. In addition, oral OTC cough and cold medicines containing antihistamines (which are clearly labeled with that word in the "uses" section of the Drug Facts label) will carry a new warning: Do not use to sedate or make a child sleepy.

Why are the labels being changed?

These changes are being made in consultation with FDA out of an abundance of caution to help address rare adverse events related to the misuse of these medicines. While the medicines themselves are safe and effective when used as directed, rare adverse events have occurred in young children from misuse and accidental ingestion. These label changes are part of an overall effort by medicine makers to encourage appropriate dosing practices.

What do I need to know as a parent?

The following tips will help you know how, when, and when not to give OTC oral cough and cold medicines to a child.

- Always follow dosing recommendations exactly and use the measuring device that comes with the medicine.
- Never give two medicines at the same time that contain the same active ingredient.
- Only give the medicine that treats your child's specific symptoms.
- If your child develops any side effects or reactions that concern you, stop giving the OTC medicine and contact a doctor immediately.
- Do not give a medicine only intended for adults to a child.
- Never use an OTC medicine to sedate or make a child sleepy.
- Never give aspirin-containing products to a child for cold or flu symptoms unless told to do so by a doctor.
- Keep all medicines out of your child's reach and sight.
- Talk to a doctor, pharmacist, or other healthcare professional if you have any questions.

What should I do if my child has a cold now?

Parents should always follow the label directions on the Drug Facts label. To address the needs of children of ages for which directions are not included on the product label, you should ask a doctor for treatment advice. As always, you should contact a doctor or other healthcare professional with any questions.

CHPA EDUCATIONAL FOUNDATION

To learn more, visit OTCsafety.org.

Facts about Children's Cough and Cold Medicines

You are likely one of the millions of parents who turn to oral over-the-counter, or OTC, cough and cold medicines when treating your children's cough and cold symptoms. As such, you may have some questions about new labeling on oral OTC cough and cold medicines for children.

The makers of OTC cough and cold medicines have created this brochure to help answer your questions.

The CHPA Educational Foundation (housed at OTCsafety.org) is the nonprofit foundation of the Consumer Healthcare Products Association, and is dedicated to providing education to consumers on the appropriate and safe use of over-the-counter medicines and nutritional supplements.

OTCsafety.org

Información sobre los medicamentos

para la tos y el resfrío, para niños

Please see reverse side for English text.

¿Son seguros los medicamentos orales OTC para la tos y el resfrío, para niños?

Sí. Los medicamentos orales OTC para la tos y el resfrío son seguros y eficaces cuando se administran de acuerdo a las indicaciones. Si bien los problemas con estos medicamentos son poco frecuentes, y en general se deben a dosis incorrectas o a niños pequeños que por curiosidad acceden a los medicamentos, los fabricantes están cambiando las etiquetas por su propia voluntad para niños menores de 4 años de edad. Las etiquetas de los medicamentos para la tos y el resfrío dirigidos a adultos no se actualizarán.

¿Estos medicamentos seguirán estando disponibles para uso infantil?

Sí, estos medicamentos orales OTC para la tos y el resfrío, para niños, aún estarán disponibles para el alivio de los síntomas de la tos y el resfrío en niños. Si bien comenzarán a aparecer nuevas etiquetas en estos medicamentos durante la temporada de tos y resfrío 2008-2009, usted puede seguir administrándoselos a niños de 4 años o más.

¿Qué dirán las nuevas etiquetas?

En sí, los medicamentos serán los mismos en los que usted ha confiado durante años para cuidar a sus hijos, pero pronto tendrán nuevas etiquetas que indicarán a los padres y cuidadores no utilizar estos medicamentos en niños de menos de 4 años. Las instrucciones actuales de dosificación para niños de 4 años y más no cambiarán. Además, los medicamentos orales OTC para la tos y el resfrío que contengan antihistamínicos (que indican claramente esa palabra en la sección de "usos" de la etiqueta de información sobre el fármaco, "Drug Facts"), contendrán una nueva advertencia: No usarlo para sedar o provocarle sueño a los niños.

¿Por qué se cambian las etiquetas?

Estos cambios se están realizando luego de una consulta con la FDA (Administración de Alimentos y Fármacos) como parte de una serie de medidas de precaución para ayudar a prevenir los poco frecuentes eventos adversos por el mal uso de estos medicamentos. Si bien los medicamentos son seguros y eficaces cuando se usan según las instrucciones, han ocurrido con poca frecuencia eventos adversos en niños pequeños, debido al mal uso y a la toma accidental. Estos cambios en las etiquetas son parte de un esfuerzo general de los fabricantes de medicamentos para lograr prácticas de dosificación adecuadas.

¿Qué debo saber como padre?

Los siguientes consejos le ayudarán a saber cómo, cuándo, y cuándo no, darle a un niño medicamentos orales OTC para la tos y el resfrío.

- Siga siempre con exactitud las recomendaciones de dosificación y use el dispositivo de medición que viene con el medicamento.
- Nunca administre al mismo tiempo dos medicamentos que contengan el mismo ingrediente activo.
- Dele a su hijo sólo el medicamento para tratar sus síntomas específicos.
- Si su hijo sufre algún efecto secundario o una reacción que le preocupen, interrumpa el medicamento OTC y comuníquese inmediatamente con un médico.
- No le dé a un niño medicamentos que son sólo para adultos.
- Nunca use un medicamento OTC para sedar o provocarle sueño a un niño.
- Nunca le dé productos que contengan aspirina a un niño, para síntomas de resfrío o gripe, a menos que un médico se lo indique.
- Mantenga todos los medicamentos fuera del alcance y fuera de la visión de su hijo.
- Hable con un médico, farmacéutico u otro profesional de la salud si tiene preguntas.

¿Qué debo hacer si mi hijo tiene un resfrío en este momento?

Los padres deben seguir siempre las instrucciones de la etiqueta de información del fármaco ("Drug Facts"). Para tratar a niños de edades que no se mencionan en las instrucciones de la etiqueta del producto, debe consultar a un médico sobre consejos de tratamiento. Como siempre, debe consultar a un médico u otro profesional de la salud si tiene preguntas.

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Para obtener más información, visite OTCsafety.org.

Información sobre los medicamentos para la tos y el resfrío, para niños

Probablemente usted sea uno de los millones de padres que recurre a los medicamentos orales (que se toman por boca) de venta libre (over-the-counter, OTC) para la tos y el resfrío, para tratar los síntomas de tos y resfrío de sus hijos. Como padre, es posible que tenga preguntas sobre las nuevas etiquetas de los medicamentos orales OTC para la tos y el resfrío, para niños.

Los fabricantes de medicamentos OTC para la tos y el resfrío han redactado este folleto para ayudar a responder a sus preguntas.

La CHPA Educational Foundation (que opera a través de OTCsafety.org) es la fundación sin fines de lucro de la Consumer Healthcare Products Association (Asociación de Consumidores de Productos para la Atención de la Salud), y se dedica a proporcionar educación a los consumidores sobre el uso adecuado y seguro de los medicamentos de venta libre y los suplementos nutricionales.

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Tip Sheet for Giving Oral OTC Cough and Cold Medicines to Children

Millions of American parents turn to oral over-the-counter, or OTC, cough and cold medicines when treating their children's symptoms. These OTC medicines have been relied upon by families for generations and are safe and effective when they are used correctly. When given as directed, OTC cough and cold medicines help treat your child's symptoms. But like all medicines, they have risks if misused.

Here's how to safely give and store these medicines:

1. Always read and follow medicine labels exactly and use the measuring device that comes with the medicine.
2. Do not give a medicine only intended for adults to a child.
3. Only give the medicine that treats your child's specific symptoms.
4. Never give two medicines at the same time that contain the same active ingredient.
5. Do not use oral cough and cold medicines for children under age 4.
6. Never use an OTC medicine to sedate or make a child sleepy.
7. Never give aspirin-containing products to a child for cold or flu symptoms unless told to do so by a doctor.
8. If your child develops any side effects or reactions that concern you, stop giving the OTC medicine and contact a doctor immediately.
9. Keep all medicines out of your child's reach and sight.
10. Talk to a doctor, pharmacist, or other healthcare provider if you have any questions.

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