Nonprescription Drug Advisory Committee Meeting

Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use

October 18 and 19, 2007

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Date: October 18, 2007

From: Office of Non-Prescription Products

To: Members of NDAC, Consultants and Guests

Subject: October 18 and 19, 2007 NDAC Meeting regarding cough and cold product use in children

Introduction

The purpose of the meeting is to discuss a Citizen Petition submitted to the Agency regarding the safety and efficacy of cold and cough products in children especially those under the age of 6 years, and to address a number of general issues raised by the Petition. Some of the topics to be discussed over the next 2 days include the following:

1) Efficacy and safety profile of these products in children;
2) The ability to extrapolate of efficacy data from adults to children of any age;
3) Dosing recommendations based on weight vs age vs other;
4) Issues of potential misuse, unintentional overdose and excessive dosing;
5) Dosing recommendations for combination products;
5) Labeling changes that may impact the safe and effective use of these products

The purpose of this memorandum is to provide pertinent background summary information and to identify points to consider as you prepare for the October 18 and 19, 2007 advisory committee meeting. The package you have been provided contains the draft agenda, the Citizen Petition and responses, reviews of safety and case reports, a discussion of the use of PK data and the E11 Guidance document ("Clinical Investigation of Medicinal Products in the Pediatric Population"), and literature addressing safety and efficacy that will be addressed during the 2 day meeting. Comments received from organizations responding to our inquiries are also included in your meeting package.

The Agency has not reached any final decisions as to actions to be taken in response to the Citizen Petition. Any review documents included in this package that contain specific recommendations should not be considered final decisions by the Agency.

Background

OTC cough and cold products are widely marketed and used by parents to treat children with symptoms of the common cold. They are available as either single ingredients or more often as combination products containing one or more of the following: nasal decongestant, expectorant, antihistamine, cough suppressant, and also an analgesic and fever reducer. In general, these products are regulated by the FDA under the OTC monograph system that can be found in the Code of Federal Regulations 21 CFR 341, or under the NDA process for new drugs. Although these products have been used in children for many years, the scientific data supporting use in children, especially those younger than two, are quite limited. Never the less, practitioners have made recommendations to parents and caregivers about treatment, using these products. Indeed some members of the committee may have recommended these products to their own patients. However, the goal of todays meeting is to objectively review the data presented and determine the appropriate path forward based on the information provided.

The Agency recently received a Citizen Petition (CP) requesting that we address whether these products should still be considered safe and effective in children less than 6 years of age. The petitioner requests that the following actions be taken:

1) labeling state that they are not to be used in children less than 6 years of age;
2) these products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold;
3) notify manufacturers of these products whose labeling uses such terms as “infant” or “baby” that such marketing is not supported by scientific evidence and that manufacturers will be subject to enforcement action .

Please see the meeting package for the complete CP.

Development of the monograph

The current doses in the directions for nonprescription cough and cold products for children were developed with input from an expert advisory panel in 1976, as part of the OTC drug review that created a specific monograph for these products.

The OTC drug review was established to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972 (date later extended to December 4, 1975). This OTC drug review is a three-phase public rulemaking process (each phase requiring a *Federal Register* publication) resulting in the establishment of standards (monographs or non-monographs) for an OTC therapeutic drug category. The first phase was accomplished by expert advisory review panels. The panels were charged with reviewing the ingredients in nonprescription drug products to determine whether

these ingredients could be **g**enerally **r**ecognized **a**s **s**afe and **e**ffective (GRASE) for use in self-treatment. The expert panels were also charged with reviewing claims and recommending appropriate labeling, including therapeutic indications, dosage instructions, and warnings about side effects and preventing misuse. The ingredients in the current OTC monograph for cough and cold symptoms were determined to be GRASE, and the panel then recommended dosing based on the information available at the time. In 1976, the external expert advisory panel consulted an additional panel of physicians about pediatric dosing. In regards to efficacy, the Advisory Panel was "aware that data on the use in children of most drugs in cough and cold products (was) negligible or nonexistent." They recognized "the extreme difficulties" associated with the conduct of clinical trials to derive "definitive pediatric drug dosage" and also recognized "the immediate need to make recommendations for pediatric dosage pending availability of such definitive data" since children were recognized to "comprise a substantial proportion of the population that receives these OTC products."

Therefore, the Advisory Panel sought the assistance of a "Special Panel on Pediatric Dosage," comprised of seven physicians. The Special Panel met with the Advisory Panel on October 31 and November 1, 1974. The outcome of the Special Panel review and meetings with the Advisory Panel was the following recommendation for fractionated dosing:

"Unless indicated contrarily, the Panel recommends the following guidelines for determining safe and effective pediatric dosages for the individual cold and cough ingredients discussed in (the ANPR):
- 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 1/4 the adult dosage;
- For children 6 to under 12 years of age, the dosage is 1/2 the adult dosage."

The Panel recommended that dosing for antihistamines not be labeled for use in children under the age of 6, except as part of the professional labeling (provided to health professionals, but not to the general public). The Panel also recommended that the terms "baby" and "infant" not be used on labeling of products that were not shown to be safe and effective in this age range. However, this wording does not appear in the final monograph.

The recommendations became part of FDA's formal regulations as a monograph on cough, cold, allergy, bronchodilator and antiasthmatic drug products. The monograph is a regulation, in Title 21 Code of Federal Regulations (21 CFR Part 341).

For additional details see the review of the monograph process in the meeting package.

Present Knowledge

The Agency has only very limited data from clinical trials showing that the ingredients in nonprescription cough and cold products described in the monograph are effective for temporarily reducing cold symptoms in children including infants, toddlers, school-aged children, and pre-teens. The Agency has not required such studies because efficacy was extrapolated from adults (see section on extrapolation of data, below, the clinical pharmacology review, and the E11 Guidance document in the meeting package), and conducting clinical trials on cough and cold products in children is difficult, especially in very young children, because self-reporting is difficult to obtain and unreliable in this age group.

Indeed, studies performed in children rarely provide evidence of efficacy for cold and cough products. This inability to establish efficacy in children is also true for other products such as drugs to treat the symptoms of allergic rhinitis. For example, an often cited review in JAMA (ref: volume 269, number 17; 1993) concludes that " No good evidence has demonstrated the effectiveness of over-the-counter cold medications in children. Further studies are required to clarify the role of these medications in children. Certain single over-the-counter medications and combinations have been shown to reduce cold symptoms in adolescents and adults." Whether efficacy can be extrapolated from adolescents to younger age groups is not clear. Notably, the Harriet Lane Handbook (a manual for pediatric house officers) provides dosing recommendations for some of these drugs, for example, brompheniramine plus pseudoephedrine for children, down to one month of age using oral drops (with the caveat "generally not recommended for treating URIs for infants"). A summary of studies in the literature addressing efficacy will be presented and a review is included in your meeting package.

However in terms of safety, over the years the Agency has become aware of isolated cases and small case series of serious adverse events, and in rare cases, deaths, reported with the use of these products in children. In January 2007, the Centers for Disease Control and Prevention, with input from the FDA, published a report in the *Morbidity Mortality Weekly Report (MMWR)* describing 3 infants, all less than one year old, who died after use of cough and cold products. The children were examined after their deaths and all had very high levels of cough and cold medicine in their blood, but no other drugs (specifically, pseudoephedrine was found in very high levels in all 3 cases), suggesting the possibility of dosing errors of some kind.

In February 2007, the Agency completed an internal review of serious and life-threatening side effects and death in children younger than six years. From 1969 through the fall of 2006, there were 54 reported cases of death just with decongestants and 69 with antihistamines, the majority in children younger than two years of age. Importantly, reporting of adverse events was not required for monograph products, nor is use data, Thus, we have no way of definitely knowing how many fatalities occurred in relation to the number of children given cough and cold products during this time, nor whether the medicine was really the only problem. It is also important that, in the cases where dosing information was available, overdose and resulting drug toxicity were often

reported. The overdosing was usually explained by mistakes in dosing for example, giving the child several combination products or measuring the dose incorrectly. In these cases the exact cause of death is difficult to determine and might be related to drugs, underlying medical condition, or a combination of both.

A review of data from the Maryland Poison Control Center shows the following: in 2004 there were approximately 1100 reports to the Maryland Poison Control Center for cough and cold products compared to, for example, 1400 reports for topical products. Of these 1100 reports, 5 were coded as having symptoms consistent with an outcome of "moderate effect" and necessitated admission to a health care facility. Four of these 5 were further coded as being unintentional-general exposure (meaning that children accidentally ingested the product). One was coded as an adverse reaction in a 4 month old who developed tachycardia after being dosed with a decongestant. All of the children had complete resolution of symptoms.

A presentation of safety data from the literature and the FDA's Adverse Event Reporting System (AERS) will be provided, and 2 reviews of safety are included in your meeting package.

Extrapolation of data from adults to children

The common cold is caused by a viral infection of the upper respiratory tract (nose, sinuses, throat). Such infections produce the familiar symptoms: congestion, excess mucous, sore throat, fever and coughing. While it is likely that the infection and the physiologic response to the infection are the same in people of all ages, so the same medicines are likely to reduce, temporarily, the symptoms in adults and children, but the doses are different. However, while the viral infection may be the same in adults and children, some have proposed that the underlying physiology and mechanisms of disease are potentially different in adults and children. These differences may include those of respiratory anatomy, maturational differences in respiratory muscles, chest wall structure, immunological responses, and finally hepatic enzymes which have an effect on drug metabolism and clearance.

In general the FDA has not required formal efficacy and safety studies in children for drugs to treat cold and cough symptoms. This decision was based on several considerations. First, the pathophysiology of the common cold is believed to be similar in adults and children, and thus extrapolating efficacy from adults to children is a reasonable approach. This approach is used for multiple classes of drugs and is not specific to the cough and cold products. Extrapolation has been the standard for drug approval in the US for many years and was codified with the passage of the Pediatric Labeling Rule in 1994. The products we are discussing today precede these initiatives and have been used for decades. Second, studies with subjective endpoints such as symptom scores, are often more difficult to perform in children. Third, these monograph cold and cough products in

particular have had a long history of use and have been felt to be very safe when used properly, even in young children. Based on the above considerations, the FDA, with input from an external advisory panel of experts, developed dosing and labeling recommendations for these products that were published in the monograph entitled " Cold, Cough, Allergy, Bronchodilator and Anti-Asthmatic Drug Products for Over-the-Counter Human Use." (see under monograph development).

A guidance document entitled "E11 Clinical investigation of medicinal products in the pediatric population" discusses the issue of extrapolation of data and the use of PK studies to establish efficacy in the pediatric population:

When a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adults efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults. If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies.

When a medicinal product is to be used in younger pediatric patients for the same indications(s) as those studies in older pediatric patients the disease process is similar and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger pediatric patients may be possible.

As an example, the committee is referred to the approval of fexofenadine for children down to the age of 6 months for the treatment of allergic rhinitis, based on PK data.

To help address some of the issues with extrapolation of efficacy using PK data, PK data available to the Agency for pseudoephedrine and chlorpheniramine found in some pediatric cold and cough products will also be presented to the committee.

Points to consider

As stated in the background section, the Agency has received a Citizen Petition requesting that action be taken to re-label cold and cough products to say that they have not been found to be safe or effective in children under the age of 6 for treatment of cough and colds, and that the products should not be used for treatment of cough and colds in children under 6 years of age. The Committee is being asked to evaluate the data that will be presented in regards to the efficacy and safety of these products. There are a number of issues that the Committee should be cognizant of during the presentations, and they will be briefly discussed here.

Efficacy and extrapolation based on PK data

First, the committee should consider whether or not the disease process is similar enough in adults and children to permit the extrapolation of efficacy from adults to children. Consider whether or not the pathophysiology of the disease is similar in adults and children Should extrapolation from adult data ever be utilized for the cough and cold indications? If yes, under what circumstances. If no, why not? Would this also apply to other indications such as allergic rhinitis.

The petitioner requests that cold and cough products not be used in children under 6. However, extrapolation has been used to allow dosing for children ages 6-12 years of age, as well as children under 6 years of age. The committee should consider whether extrapolation to any age not be allowed. This decision will clearly impact the remainder of the discussion.

The committee will need to consider that if we cannot extrapolate from adults to children, then clinical efficacy studies will be needed in children. What are the difficulties associated with conducting these types of studies to demonstrate the efficacy of cough and cold products in children? How can these difficulties be addressed? Are there alternative approaches?

If the disease processes are considered similar enough in adults and children to allow extrapolation, then based on dosing recommendations found presently in the cold and cough monograph, should we make any changes to those recommendations? Acknowledging inherent problems with dosing based on age, nevetheless, does dosing by age (and taking a fraction of the adult dose) remain a viable approach especially in light of the extensive history of use of these products over decades and the fact that these products are used without a learned intermediary such as a physician? One possible approach incorporating age adjusted dosing would involve smaller age intervals for example dosing recommendations for children ages 0-2, 2-4, 4-6, 6-10 etc. If this approach is not acceptable, then what approach should be taken (weight based dosing etc) in order to provide dosing recommendations that can be easily understood by the consumer?

Safety

Second, Can we conclude that a reasonable safety profile has been established for these products in children? Is the safety profile such that we can continue to use these products in children of all ages? If not, what populations require additional data? Based on the reported cases of serious AEs, do we need more safety data for the various populations at risk (age groups)?

The safety discussion in the petition focuses on cases of misuse, unintentional overdose, and excessive dosing of OTC cough and cold drug products. The petition does not address the safety of OTC cough and cold drug products for children under the age of 6 when used in accordance with the labeled instructions and under a physicians care. Should dosing for children under 6 years of age (under 2 years of age) ever be permitted?

Are adverse events generally associated with "correct" use or rather with misuse and excessive dosing? Safety issues may be related to intrinsic factors such as to differences in an individuals' ability to metabolize and eliminate drugs, to other individual factors (idiosyncratic), or to factors extrinsic to the individual such as occurs with accidental dosing errors. Do intrinsic factors play a role here or are safety issues rather related to extrinsic factors such as dosing errors? If intrinsic factors play a role, would dosing based on other approaches lead to safer use of these products? For example, is dosing based on weight or body surface area a feasible approach for OTC products or is dosing based on age an acceptable approach in terms of safe use of these products?

In regards to extrinsic factors, in a number of cases of death associated with the use of cold and cough products, post-mortem levels were elevated, although the significance of post-mortem levels, and how they related to pre-mortem levels, is not always clear. However, in those cases where elevated levels of drug were found post-mortem can we identify whether these were due to unintentional overdose due to caregiver error in measuring the product, incorrect use of dosing devices that might have led to dosing error, use of multiple combination products (see below), to use of products with identical ingredients but different names, or to some other extrinsic factors? If so, what actions should be taken to address each of these areas of potential concern that contribute to the issue of unintentional overdosing?

Many products for the treatment of cold and cough are combination products. These combination products may contain overlapping ingredients. Also, these combination products sometimes present a challenge in identifying an optimal dosing schedule because the doing schedules of individual ingredients may not be the same. In terms of both safety and efficacy, how can we address the extensive use of combination products and appropriate dosing?

Labeling

Third, currently the directions for all OTC cough and cold products instruct a parent to "consult a doctor" for children under two years of age. Additionally, the directions for OTC antihistamines instruct a parent to "consult a doctor" for children under 6 years of

age. There is professional labeling available for antihistamines for children between 2 and 6 years of age. The “consult a doctor” or “ask a doctor” directions have permitted physicians to make clinical judgments about whether a specific OTC product was appropriate for a child under their care. However, the petition requests the following label changes: *These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold. These products should not be use for treatment of cough and cold in children under 6 years of age.*

The labeling proposed in the petition may possibly change this option for physicians so that they will not be able to prescribe OTC cough and cold products in children less than 6 years old. What impact would the label change that says do not use for children less than 6 years of age, have on the treatment of children with cough and colds. Can we better define the meaning of the statement “ask your doctor”? For example, would additional wording such as “do not use unless you ask your doctor first” be clearer to the consumer? Are there any other labeling changes that can address the potential for problems related to the use of multiple medications that have similar ingredients that may lead to accidental overdosing or other preventable errors in dosing?

March 1, 2007

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services, Room 1-23
12420 Parklawn Dr., Rockville, MD 20857

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition under 21 CFR Sec. 10.30. This Citizen Petition requests the Commissioner of Food and Drugs to take the following action with respect to 21 CFR 341, the Final Monograph (FM) for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use.

ACTION REQUESTED

The Petitioner requests the Commissioner to:

1. Provide a statement to the public explaining that over-the-counter antitussive, expectorant, nasal decongestant, antihistamine and combination cough and cold products have not been shown to be safe and effective for the treatment of cough and cold in children under six years of age.

2. Notify manufacturers of these products whose labeling 1) uses such terms as "infant" or "baby," or 2) displays images of children under the age of 6 that:

   a. Such marketing is not supported by scientific evidence; and

   b. Manufacturers will be subject to enforcement action at any time.

3. Amend 21 CFR 341 to require that labeling for over-the-counter antitussive, expectorant, nasal decongestant, antihistamine, and combination cough and cold products state:

   a. These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold.

   b. These products should not be used for treatment of cough and cold in children under 6 years of age.

STATEMENT OF GROUNDS

I. BACKGROUND

The class of over-the-counter cold, cough, allergy, bronchodilator and antihistamine (cough and cold preparations) medications are widely marketed and widely used for children. Under the law, they are classified as "generally recognized as safe and effective." Yet, for treatment of cough and cold for children under six years of age, these products have not been shown to be safe, have not been shown to be effective, and are not generally recognized as safe and effective.

II. USE AND MARKETING OF OVER-THE-COUNTER COUGH AND COLD MEDICATIONS

Over-the-counter cough and cold medications are widely used by young children. Young children are disproportionately vulnerable to the common cold, with the average child suffering from 6-10 colds per year.

In 1994, researchers reported in the *Journal of the American Medical Association* that in a specific 30-day span, 35.8% of all 3 year-old children in the United States were given over-the-counter cough and cold preparations.[1] And in 1990 alone, Americans spent nearly $2 billion on these medications.[2]

In a typical drugstore, over 30 separate cough and cold preparations are marketed to parents for use in children. Products advertised for use in toddlers and young children are typically liquid formulations or chewable tablets. These include dextromethorphan and guaifenesin for cough as well as chlorpheniramine maleate and phenylephrine for nasal congestion.

Other products are labeled as "infant" formulations, display images of babies and infants, and include oral droppers or syringes to dispense medications to children too young to drink from spoons or cups. Examples include products containing acetaminophen and phenylephrine marketed for cold; products containing dextromethorphan and guaifenesin marketed for cough.

Manufacturers and trade associations justify marketing practices by referencing FDA approval of their products. In a recent letter, the Consumer Healthcare Products Association wrote that "the U.S. Food and Drug Administration deems OTC cough and cold medicines safe and effective, provided they are used as directed."[3]

III. FDA HISTORY

The Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act established that all marketed drugs must demonstrate both efficacy and safety. In order to review safety and efficacy data for the thousands of over-the-counter drugs already on the market, the FDA approved each class of drugs through a three-step review process.

The approval process, which was outlined in the Code of Federal Regulations, Title 21, Part 330, included input from an expert advisory panel, solicitation of public comment on proposed rules, and establishment of a monograph outlining conditions of use for approved drugs. Cough and cold preparations were approved through this process, verifying that the FDA found that these medications are "generally recognized as safe and effective and not misbranded." (21 CFR 340.1)

During this process, however, FDA never conducted an evaluation of safety and efficacy of cough and cold preparations in young children. To the extent the agency has commented on the pediatric population, it has said that little or no data are available.

The approval process for cough and cold preparations began in 1976, when the FDA published an Advance Notice of Proposed Rulemaking containing the findings of the pediatric advisory panel convened to assess these medications. While acknowledging that "pediatric patients comprise a substantial proportion of the population that receives these [over-the-counter] products," the Panel concluded that "data on the use in children of most drugs in [cough and cold preparations] are negligible or nonexistent." (41 FR 38333)

Moreover, the Panel objected to the marketing of these products using the terms "baby" or "infant," stating "that the labeling terms 'baby' and/or 'infant' on [cough and cold preparations] implies that such products have been approved for use in children under 2 years of age." (41 FR 38333) The Panel recommended that these medications not be marketed to children under two at all. (41 FR 38333)

Between 1977 and 2005, the FDA released Proposed Rules for subcategories of cough and cold preparations. The Proposed Rules address public comments submitted to the FDA in response to the initial Advance Notice of Proposed Rulemaking. In a review of the hundreds of comments submitted for FDA review, we identified only four that dealt substantially with the safety or efficacy of cough and cold preparations in a pediatric population.

In 1982, a comment "disagreed with limiting the OTC use of ipecac syrup as an expectorant to Children 6 years of age and older," claiming that ipecac had a history of safety when used in children ages 2 to 6. The FDA stated that the limitation would remain, referencing the lack of data supporting efficacy of ipecac and the lack of any safety data in children. (47 FR 30007)

One comment in 1983 "objected to the use of codeine antitussives in children." (48 FR 48587) In response, the FDA asked the American Academy of Pediatrics to make recommendations, and ultimately moved the classification of codeine antitussives for children ages 2 to 6 from general labeling to professional labeling.

Another comment in 1983 asked that the FDA take a "careful look" at "antitussive medications currently marketed OTC, especially dextromethorphan." The

FDA responded that, "While the potential for accidental overdosing and subsequent effects must be considered for any drug, in the case of dextromethorphan, the potential for toxicity to occur from accidental overdose is very low." (48 FR 48581)

In 1985, a comment raised "concern[s] about camphor poisoning in children." The FDA responded by referring to the agency's position on topical camphor products, contained in the over-the-counter external analgesic monograph. At the time, camphor as a nasal decongestant was not yet approved by the FDA. (50 FR 2223)

The only other specific evaluation of pediatric toxicity data cited in the Proposed Rule reports comes from data on diphenhydramine contained in the External Analgesic Tentative Final Monograph. After reviewing numerous case reports on toxic psychosis experienced in children using topical and oral diphenhydramine, the FDA proposed warning statements on diphenhydramine toxicity to be included in all labeling. (62 FR 45767)

In none of these cases did FDA provide an overall assessment of safety or efficacy in young children based on pediatric data.

FDA finalized its rules from 1976 to 2006 without any additional analysis on safety or efficacy for young children.

The result is that since 1976, FDA has neither conducted nor presented any review of evidence on safety or efficacy data for cough and cold preparations in young children. The current cough and cold preparation monograph still provides no dosing guidelines for children under 2 in general public dosing information, and requires that manufacturers direct parents to consult a physician before administering the products to children in this age range.[4]

IV. RECENT EVIDENCE

In the time since the approval process for cough and cold preparations began 30 years ago, a growing body of evidence has demonstrated that these products in young children are not effective, not safe -- and not generally accepted as such. The literature review provided in this Petition includes case studies, randomized controlled trials, meta-analyses of clinical trials, and clinical guidelines. Inclusion of this data in the body of evidence used by the FDA in its ongoing assessment of over-the-counter drug safety and efficacy is essential to protect children from ineffective and potentially dangerous medications.

A. Not Effective

In 1993, a review in the *Journal of the American Medical Association* of clinical trials assessed over-the-counter cough and cold preparations.[5] At the time, only two studies had specifically targeted preschool children, neither of which had demonstrated that the medications were associated with symptom relief.

Nearly a decade later, a review in the *Archives of Disease in Childhood* surveyed six randomized controlled trials in children with acute cough associated with upper respiratory infection.[6,7,8,9,10,11,12] Again, antitussives, antihistamine-decongestant combinations and antihistamines were found to be no more effective than placebo in relieving symptoms of acute cough in children. The authors concluded, "We cannot recommend OTC cough medicines as a first line treatment for children with acute cough."

A recent subjective study examined the impact of diphenhydramine and dextromethorphan on cough frequency, quality of sleep for the child or parent, cough severity and bothersome nature of cough. It found that neither medication was superior to placebo in providing nocturnal symptom relief.[13]

A recent meta-analysis published in the Cochrane Review, a highly respected evidence-based review journal, found that insufficient data and variable study quality continues to complicate efforts to clarify efficacy of over-the-counter cough and cold preparations in symptomatic care of children or adults with upper respiratory infections. Seven well-designed studies in children were included in their final review.[7,9,10,12,14,15]

B. **Not Safe**

Although typically considered safe by parents and pediatricians, misuse of over-the-counter cough and cold preparations has led to significant adverse effects in children under 6 years of age. While some of these effects have been well documented, such as the risk of hemorrhagic stroke that led to the FDA removal of phenylpropanolamine from the market in 2000,[16,17] many are under-reported and unpublicized.

We recognize that safety is a relative concept, and that the risk of adverse effects must be balanced against efficacy in the drug approval process. In the case of cough and cold preparations for young children, the lack of efficacy means there is no justification to tolerate a real risk of severe side effects.

Specific reported toxicities among young children vary with the active ingredient of the medication. In 1995, Joseph and King published a case report of a 3 year-old child who experienced an acute dystonic reaction following ingestion of recommended doses of a product containing diphenhydramine.[18]

Numerous cases of unintentional overdosage of cough and cold preparations have been reported. In 1998, excessive dosing of a medication containing dextromethorphan and pseudoephedrine led to psychosis and ataxia in a 2 year-old child.[19] Overdoses of combination drug products containing these two active ingredients have also been linked to sinus tachycardia, left ventricular dysfunction, and cardiopulmonary arrest in children under 6 years of age.[2] Overdoses of combination decongestant products including pseudoephedrine have also been associated with several case reports involving visual

hallucinations in children under 5 years old,[20] and pseudoephedrine alone has been linked to agitation, hypertension and seizures.[21]

In an analysis of 3.8 million exposure incidents involving children under 6 years of age that were made to the American Association of Poison Control Centers between 1985 and 1989, seventy-two children under 6 years of age were noted to have "major effects" associated with overdoses of cough and cold medications, defined as an effect which was life-threatening or left residual disability. Four children died.[22]

In 2004, approximately 900 children under the age of 5 overdosed on OTC cough and cold medications in Maryland.[23] And over the last five years in Baltimore City, the medical examiner has linked at least four deaths of children under 4 years old to unintentional overdoses of OTC cough and cold combination drug products.[24]

The Centers for Disease Control and Prevention recently released a study associating unintentional overdoses of cough and cold preparations with the deaths of three infants in 2005. The study cited "the risks for toxicity, absence of dosing recommendations, and limited published evidence of effectiveness of these medications in children aged <2 years."[25]

C. Not Generally Recognized as Safe and Effective

In light of the growing evidence for lack of efficacy and risk of toxicity, a number of professional organizations and agencies have spoken out against use of OTC cough and cold medications in children. In the face of this opposition, it is simply not credible for FDA's position to remain that these products are "generally recognized as safe and effective" for children under six.

In a policy statement released in 1997, the American Academy of Pediatrics reviewed dosing guidelines, clinical trials, and available data on clearance and metabolism of antitussive agents. After finding a lack of evidence to support the efficacy or safety of narcotics or dextromethorphan in children, the Academy determined that "indications for their use in children have not been established." The Academy further recommended that parents be educated "about the lack of proven antitussive effects and the potential risks of these products."[26]

In 2006, the American Academy of Chest Physicians published clinical practice guidelines that concluded, "In children with cough, cough suppressants and other over-the-counter cough medicines should not be used as patients, especially young children, may experience significant morbidity and mortality."[27]

In Baltimore City, pediatric leaders recently released a statement on over-the-counter cough and preparations (attached). The statement concluded, "Since the evidence shows that these products have no benefit, and the side effects may indeed cause harm, we recommend that families be aware of these risks and not use over-the-counter cough and cold medications for children ages five and under."

Signers of the statement included the chiefs of pediatrics at St. Agnes Hospital, Franklin Square Hospital, Harbor Hospital, Johns Hopkins Bayview, Johns Hopkins Hospital, Mercy Medical Center, Sinai Hospital, Union Memorial Hospital, and the University of Maryland Medical Center. Also signing were the head of the Maryland chapter of the American Academy of Pediatrics (on behalf of the chapter), and the Baltimore City Commissioner of Health.

Recently, the Centers for Disease Control and Prevention advised that "parents and other caregivers should not administer cough and cold medications to children in this age group without first consulting [a] health-care provider." Even FDA's sister agency does not see these products as "generally recognized as safe and effective."[25]

V. CONCLUSION

Over the counter cough and cold preparations are neither safe nor effective for use in young children. FDA has never conducted an appropriate analysis to support their widespread use, and expert organizations agree that they are ineffective and pose a risk to health. Deaths and serious injuries have been linked to misuse of these medications.

Based on this scientific record, we petition that the FDA:

1. **Provide a statement to the public explaining that over-the-counter antitussive, expectorant, nasal decongestant, antihistamine and combination cough and cold products have not been shown to be safe and effective for the treatment of cough and cold in children under six years of age.**

Education is an essential component to patient safety. A public statement explaining the lack of evidence for use of cough and cold preparations in children under 6 years of age will allow parents to make informed decisions about the types of medications they choose to give to their children.

2. **Notify manufacturers of these products whose labeling 1) uses such terms as "infant" or "baby," or 2) displays images of children under the age of 6 that:**

   a. **Such marketing is not supported by scientific evidence; and**
   b. **Manufacturers will be subject to enforcement action at any time.**

For products not shown to be safe or effective for children under 6 years of age, marketing containing images or terms that encourage use in this age range is misleading.

3. **Amend 21 CFR 341 to require that labeling for over-the-counter antitussive, expectorant, nasal decongestant, antihistamine, and combination cough and cold products state:**

a. **These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold.**
b. **These products should not be used for treatment of cough and cold in children under 6 years of age.**

Appropriate labeling is necessary to ensure that parents are aware of the lack of efficacy and possible toxicity of these medications.

ENVIRONMENTAL IMPACT STATEMENT

According to 21 CFR Sec. 25.31(a), this Petition qualifies for a categorical exclusion from the requirement that an environmental impact statement be submitted.

ECONOMIC IMPACT STATEMENT

According to 21 CFR Sec 10.30(b), an economic impact statement is to be submitted only when requested by the Commissioner following reviewing of this Petition.

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 15, 2007

From: Cough/Cold Pediatric Dosing Review Team

Through: Office of Nonprescription Products

To: Members of Nonprescription Drug Advisory Committee, Consultants and Guests

Subject: FDA Discussion of Pediatric Cough/Cold Products

This memo provides information on how FDA evaluates the safety and effectiveness of nonprescription drugs.

How does FDA evaluate nonprescription drug products?
The safety and effectiveness of nonprescription drugs is evaluated by one of two mechanisms, the New Drug Approval (NDA) process or the Over-the-Counter (OTC) Drug Review.

NDA process
The NDA review process evaluates the safety and effectiveness of individual drug products. Drug products that are not generally recognized as safe and effective (not GEASE) by experts qualified by scientific training and experience or that are not eligible for evaluation under the OTC Drug Review are evaluated by this process. NDA products may not be marketed without Agency approval, and once approved must comply with post-marketing reporting requirements that include adverse event reporting and the submission of any information that may have a bearing on the safe and effective use of the drug. The review process is confidential and approval may result in a period of marketing exclusivity.

OTC Drug Review
The OTC Drug Review evaluates the safety and effectiveness of active ingredients for specific nonprescription drug categories, e.g., chlorpheniramine maleate for antithistaminic use. It is an evaluation of marketed products. Only products meeting specific marketing requirements are eligible for the Review.

This OTC drug review grew out of the 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act (the Act) requiring that all drug, prescription and OTC, be shown to be safe and effective before marketing. Under the original Act of 1938, drugs had only to be proved safe before they were offered for sale. The 1962 amendments also

provided for an effectiveness review of all drug, including those previously approved for safety.

When the 1962 Drug Amendments Act was published, there were approximately 300,000 drug products available to consumers without prescription. When FDA took a sample review of 500 OTC drug products, only 25 percent were found to be effective for one or more of their intended uses. Thus, an extensive review of OTC drugs was initiated in 1972. Only products meeting specific marketing requirements are eligible for the Review. For a product to be eligible it must have been marketed in the United States prior to the initiation of the review (May 11, 1972). This date was subsequently extended to December 4, 1975.

In this drug review process, FDA looks at ingredients rather than individual products and grouping these ingredients into more than 80 classes of drugs, also called "Therapeutic Categories". These drug classes range from acne drug products to weight control drug products and include about 800 significant active ingredients. Ingredients being reviewed are classified in one of three ways:

Category	Description
Category I	Generally recognized as safe and effective and not misbranded (GRASE)
Category II	Not generally recognized as safe and effective or is misbranded (Not GRASE)
Category III	Insufficient data available to permit classification. Allows a manufacturer an opportunity to show that the ingredients in a product are effective, and, if they are not, to reformulate or appropriately re-label the product

FDA also reviews labeling because the safety and effectiveness of OTC drug products depend not only on the ingredients but also on clear and truthful labeling that can be understood by consumers.

Unlike the NDA process, products may continue to be marketed while undergoing evaluation. However, this marketing is subject to the risk that some aspect of the product, e.g., active ingredient, dose, or labeling, may not be found to be GRASE and could no longer be marketed with these conditions.

Where the NDA process is strictly confidential, the OTC Drug Review is accomplished through the multistep public notice and comment rulemaking shown below.

OTC Drug Review Step	Process
Expert **Advisory Review Panel** evaluation	Evaluation of data submitted in response to FDA's call for data on an OTC drug product category, e.g., cough/cold drug products. Panel deliberations are public.
Advance Notice of Proposed Rulemaking (ANPR)	Publication of the Panel's recommendations along with FDA's proposed regulation based on these recommendations with an opportunity for comment and submission of new data.
Tentative Final Monograph (TFM)	FDA's proposed regulation based on the Panel's recommendations and public comment and new data received with an opportunity for comment and submission of new data.
Final Rule (FR)	FDA's regulation – often known as the monograph which is published in the Federal Register and in the Code of Federal Regulations.

The end product of the Review is a final regulation that describes active ingredients, their dose, and labeling conditions that are recognized as safe and effective for a specific OTC use. Some final rules also include final formulation testing requirements and protocols to demonstrate the effectiveness of specific product formulations. Products that are compliant with a final regulation may be marketed without prior FDA approval. Manufacturers are not required to comply until the effective date of the final regulation. No marketing exclusivity is conferred under this process.

Pediatric Dosing
For
Commonly Used Cold/Cough Ingredients

Pediatric Dosing
Antihistamine/Antitussive/Nasal Decongestant
(Commonly used ingredients)

Category	Ingredients	Pediatric dosing				Efficacy Data (September 9, 1976 ANPR+)
		Adult and children 12 years of age and above	**6 to under 12 years of age**	**2 to under 6 years of age**	**Under 2 years of age**	
Antihistamine	Brompheniramine Maleate	4 mg q 4-6 hours, not to exceed 24 mg in 24 hours, or as directed by a doctor	2 mg q 4-6 hours, not to exceed 12 mg in 24 hours, or as directed by a doctor	Consult a doctor ***1 mg q 4-6 hours, not to exceed 6 mg in 24 hours***		**7 studies reviewed.** In one study, 23 **children** ages 2 mths to 2 years at a dosage of 0.2 mg to 0.5 mg/lb in 24 hours divided into 3 doses for treatment of PR. Most of these patinets had received other antihistamines without benefit. In addition, all have been instructed in environmental control measures and many were receiving injections of allergenic extracts. Panel concluded that evidence of effectiveness for children was insufficient.
	Chlorpheniramine Maleate	4 mg q 4-6 hours, not to exceed 24 mg in 24 hours, or as directed by a doctor	2 mg q 4-6 hours, not to exceed 12 mg in 24 hours, or as directed by a doctor	Consult a doctor ***1 mg q 4-6 hours, not to exceed 6 mg in 24 hours***		**8 studies reviewed.** The Panel concluded that 4 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis.
	Diphenhydramine Hydrochloride	25 to 50 mg q 4-6 hours, not to exceed 300 mg in 24 hours, or as directed by a doctor	12.5 to 25 mg q 4-6 hours, not to exceed 150 mg in 24 hours, or as directed by a doctor	Consult a doctor ***6.25mg q 4-6 hours, not to exceed 37.5 mg in 24 hours***		**17 studies reviewed.** The Panel's opinion concerning effectiveness in the treatment of allergic rhinitis rests on wide usage over a period of 30 years.
Antitussive	Codeine For dispensing to children under 2 years of age, a special measuring device should be used.	10 to 20 mg q 4-6 hours, not to exceed 120 mg in 24 hours, or as directed by a doctor	5 to 10 mg q 4-6 hours, not to exceed 60 mg in 24 hours, or as directed by a doctor	***1 mg/kg/day in divided dose q 4-6 hours. *2 years ≤ 12 mg in 24 hours. *3 years ≤ 14 mg in 24 hours. *4 years ≤ 16 mg in 24 hours, 5 years ≤ 18 mg in 24 hours.***	****Not recommended***	**9 studies reviewed.** No well controlled studies in children. Dosing is based on the general experience of a Pediatric Panel. Accepted the effectiveness in cough due to upper respiratory infection, may, in large measure, be extrapolated from the information on antitussive activity in chronic cough.

* bold italic = professional labeling dosing

+ANPR = Advance Notice of Proposed Rulemaking

Pediatric Dosing
Antihistamine/Antitussive/Nasal Decongestant
(Commonly used ingredients)

Category	Ingredients	Pediatric dosing				Efficacy Data (September 9, 1976 ANPR+)
		Adult and children 12 years of age and above	**6 to under 12 years of age**	**2 to under 6 years of age**	**Under 2 years of age**	
Antitussive	Dextromethorphan	10 to 20 mg q 4 hours or 30 mg q 6-8 hours, not to exceed 120 mg in 24 hours, or as directed by a doctor	5 to 10 mg q 4 hours or 15 mg q 6-8 hours, not to exceed 60 mg in 24 hours, or as directed by a doctor	2.5 to 5 mg q 4 hours or 7.5 mg q 6-8 hours, not to exceed 30 mg in 24 hours, or as directed by a doctor	Consult a doctor	**19 studies reviewed.** Studies demonstrated effectiveness is comparable to codeine on mg-for-mg basis for cough suppression. Cough/Cold Panel concluded effective because of its low order of toxicity.
	Diphenhydramine Hydrochloride	25 to 50 mg q 4-6 hours, not to exceed 300 mg in 24 hours, or as directed by a doctor	25 mg q 4 hours, not to exceed 150 mg in 24 hours, or as directed by a doctor	Consult a doctor ***6.25mg q 4 hours, not to exceed 37.5 mg in 24 hours***		**12 studies reviewed.** In man, experimentally induced sough employing a controlled double-blind crossover design in which both the 25 mg and 50 mg dosed of diphenyhdramine HCl produced significant cough suppression equivalent to 15 mg of codeine.
Nasal Decongestant	Pseudoephedrine	60 mg q 4-6 hours, not to exceed 240 mg in 24 hours	30 mg q 4-6 hours, not to exceed 120 mg in 24 hours	15 mg q 4-6 hours, not to exceed 60 mg in 24 hours	Consult a doctor	**5 studies reviewed.** A double-blind subjective study in **children** showed pseudoephedrine to be better than placebo in allergic respiratory disease and possibly also in non-allergic respiratory conditions, but no statistics are given.
	Phenylephrine Hydrochloride	10 mg q 4 hours, not to exceed 60 mg in 24 hours	5 mg q 4 hours, not to exceed 30 mg in 24 hours	2.5 mg q 4 hours, not to exceed 15 mg in 24 hours	Consult a doctor	**14 studies reviewed.**

* bold italic = professional labeling dosing

+ANPR = Advance Notice of Proposed Rulemaking

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 6, 2007

TO: Andrea Leonard-Segal, M.D., M.S., Director
Division of Nonprescription Clinical Evaluation

THROUGH: Rosemary Johann-Liang, MD, Deputy Director
For Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

FROM: Gita Akhavan-Toyserkani, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation

SUBJECT: Infant mortality associated with the use of cough and cold medications
Drugs: decongestants (pseudoephedrine, phenylephrine, ephedrine) and antihistamines (diphenhydramine, brompheniramine, chlorpheniramine)

RCM #: 2006-122

1. EXECUTIVE SUMMARY

This consult is in response to a request from the Division of Nonprescription Clinical Evaluation (DNCE) to review the Adverse Event Reporting System (AERS) database for reports of infant mortality associated with the use of pseudoephedrine, phenylephrine, ephedrine, diphenhydramine, brompheniramine, and chlorpheniramine. The Center for Disease Control and Prevention (CDC) recently issued a Morbidity and Mortality Weekly Report (MMWR) article describing three deaths in U.S. infants aged less than 12 months associated with cough and cold medications.[1] As a result of these deaths, the CDC is collaborating with DNCE and the Division of Drug Risk Evaluation (DDRE) to review adverse event (AE) reports submitted to the Agency through the MedWatch program regarding the use of decongestants and antihistamine in children.

Over-the-counter (OTC) and prescription cough and cold medicines containing decongestants and antihistamines are prescribed widely by general pediatricians for the

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[1] Centers for Disease Control and Prevention. 2007. Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005. *M.M.W.R.* 56 (01);1-4.

symptoms of the common cold.[2] More than 800 cough and cold preparations, to include pediatric preparations, are available in the United States.[3] However, current data is limited for children less than 2 years of age with regard to efficacy and safety of cough and cold medications. Several articles regarding the safety and efficacy of OTC cough and cold medicines in children have been published.[4,5,6] Published controlled trials have shown that antihistamine-decongestant combination products are no more effective for symptoms of upper respiratory tract infection than placebo in young children.[7,8,9,10,11]

Pseudoephedrine, phenylephrine, and ephedrine are nasal decongestant drug products listed in the OTC monograph. Currently, the OTC dosing recommendations for decongestants start at age 2 years and above, with the statement to "consult a physician" for dosing recommendations below 2 years of age. Diphenhydramine, brompheniramine, and chlorpheniramine are first generation antihistamine drug products listed in the OTC monograph. The OTC dosing recommendations for antihistamines start at age 6 years and above, with the statement to "consult a physician" for dosing recommendations below 6 years of age.

In this consult we were asked to 1) analyze pediatric adverse event reports in children 6 years of age and younger, 2) address whether the safety concerns were related to the prescription or OTC use of these products, and 3) assess whether the adverse events were related to the use of a single product or multiple products containing the same ingredients. An AERS search was conducted for reports of pediatric fatalities $\leq$ 6 years of age between 1969 and September 13, 2006 associated with the use of decongestants **(pseudoephedrine, phenylephrine, ephedrine)** and antihistamines **(diphenhydramine, brompheniramine, chlorpheniramine)**. Cases were limited to U.S. domestic cases and

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[11] Smith MBH, Feldman W. Over-the-counter cold medications: A critical review of clinical trials between 1950 and 1991. Journal of the American Medical Association. 1993;269(17):2258-63.

included reports associated with single and combination products as well as OTC and prescription products.

There are many limitations of quantitatively analyzing a spontaneous reporting database such as AERS. One limitation is that an adverse event report may contain concomitant use of other medications and/or multiple ingredient products, and therefore, a clear drug-event association is often difficult to establish. The decongestants and antihistamines discussed in this consult are found in many OTC preparations either as single-ingredient preparations, or more commonly in combination, with acetaminophen and/or ibuprofen. Other limitations include underreporting and the length of time the product has been on the market. Under 21 CFR part 341 there are no reporting requirements for OTC monograph products, which makes it especially difficult to obtain a true number of adverse events (numerator) for these products. Furthermore, drug exposure data (denominator) is not available for OTC products and so the quantification of risk assessment is not possible.

The highlights of AERS results for decongestants review is summarized as follows. There were 46 unique domestic fatal cases associated with **pseudoephedrine**, four with **phenylephrine**, and four with **ephedrine**. The majority of the cases occurred in children less than 2 years of age, of which 43 cases were reported in children less than 1 year of age. Nine cases were reported in children between 2-6 years of age. Dosing was available in 17 of the 46 pseudoephedrine cases; a single dose ranged from 3- 94 mg, with a median of 15 mg (these doses were all reported in children less than 2 years of age). Among the decongestant cases where time to onset was available, the majority were less than 5 days. Among the pseudoephedrine cases 15 reported an onset of less than 1 day to include 5 cases that reported an onset after 1 dose. Overdose and drug toxicity were common adverse events reported in these cases: and the manner of overdose included use of multiple cold/cough products, medications errors, accidental exposures, and intentional overdose. There were a total of 28 cases with a reported postmortem level among the decongestant cases; 24 of which were above the adult therapeutic level. The upper range for reported postmortem pseudoephedrine and ephedrine level was 30-fold and 5-fold higher than the adult therapeutic level, respectively. There were no postmortem levels provided among the phenylephrine cases. Cases were associated with both OTC and prescription products to include unapproved prescription products. About 46 % of the pseudoephedrine cases with a reported trade name were associated with a non-approved prescription product.

The highlights of AERS results for antihistamines review is summarized below. There were 33 unique fatal domestic cases associated with **diphenhydramine**, 9 **brompheniramine**, and 27 **chlorpheniramine**. The age range and average age was slightly higher among the antihistamine cases than decongestants cases; especially, among the chlorpheniramine cases. Among the antihistamine cases, 41 cases were reported in children less and 2 years of age and 28 were reported in children between 2-6 years of age. These cases provided limited information in regards to dosing and time to onset. Overdose and drug toxicity were common adverse events reported in these cases: and the manner of overdose included use of multiple cold/cough products, medications

errors, accidental exposures, and intentional overdose. There were a total of 28 cases with a reported postmortem level among the antihistamine cases; 18 of which were above the adult therapeutic level. The upper range for reported postmortem diphenhydramine, brompheniramine, and chlorpheniramine level was approximately 13-fold, 2-fold, and 10-fold higher than the suggested adult therapeutic level, respectively. Cases were associated with both OTC and prescription products.

The AERS cases demonstrate that the administration of cough and cold medicines in children less than 2 years of age could lead to serious adverse events including death. Since there are no dosing recommendations as per the OTC monograph for children under the age of 2, most of these cases could be considered off-labeled use. The most common adverse event implicated with these cases was drug overdose or drug toxicity. The manner of overdose was found to be due to accidental overdoses as well as intentional overdoses. Accidental overdose of both prescription and OTC cough and cold products were related to multiple product use, medication error, uncertainty in dosing, accidental exposure, and other preventable mistakes. Other factors contributing to accidental overdose may be as a result of drug interactions, or diseases that increase sensitivity to sympathomimetic and anticholinergic agents.

Medication error due to lack of proper dosage guidelines for the cough and cold products may be contributing to overdose in children less than 2 years of age. Parents and caregivers may not be aware of the duplication of ingredients and the potential risk of overdose when using multiple products. Furthermore, parents may be misinformed that OTC cough and cold medications intended for children 6 years and above are also safe in younger children and infants. Dosing suggestions for these products are often published by the manufacturers and are extrapolated from adult dosing. As in the case of the unapproved prescription product, Rondec®, the average recommended doses are age based. Age based dosing may lead to increased risk of overdose, especially in infants who are below the average weight or are born premature. Furthermore, most cough and cold preparations are combinations of at least 2 or more ingredients, and it is unclear as to which active ingredient the dose is based on.[12] There is also the potential for confusion between the children's cough/cold products and the infants' concentrated drops (higher concentration) in regards to the dosing regimen that could lead to adverse events. Finally, some of the products are unapproved products (e.g. Rondec®, Cardec DM ®, Tussend®, etc.) and the quality of these products is unknown. When manufacturers change the formulation of a product, new preparations of a particular cough and cold product should also be easily distinguished from existing preparation.

In conclusion, the AERS postmarketing data suggest that the use of prescription and OTC cough and cold medication in younger children, particularly in children less than 2 years of age, could result in fatal overdoses. Therefore, we recommend an educational campaign which addresses proper education about cough and cold products; in particular, the risks of using these products in children less than 2 years of age and the duplication of ingredients with the potential risk of overdose when using multiple products. In view of

[12] Bhatt-Mehta V. Over-the-counter cough and cold medicines: Should parents be using them for their children? Annals of Pharmacotherapy. 2004;38(11):1964-6.

the current data that lacks the evidence of efficacy and the potential for toxicity, the labeling of cough and cold products (both prescription and OTC) should include prominent language to describe the risk of overdose in children. Also, we recommend that the current OTC dosing recommendation which suggests to "consult a physician" for decongestants in patients under 2 years of age and for antihistamines in patients under 6 years of age should be reconsidered. This statement is confusing and appears to contribute to medication errors which can result in fatal overdoses. We suggest that the revised wording state that dosing is not recommended in these age groups due to the lack of evidence of efficacy and safety concerns. Further, a timely forum among stakeholders is recommended to discuss making only single ingredient products available for pediatric formulations.

TABLE OF CONTENTS

2. BACKGROUND

This consult is in response to a request from the Division of Nonprescription Clinical Evaluation (DNCE) to review AERS reports of infant mortality associated with the use of pseudoephedrine, phenylephrine, ephedrine, diphenhydramine, brompheniramine, and chlorpheniramine. The Center for Disease Control and Prevention (CDC) recently issued a Morbidity and Mortality Weekly Report (MMWR) article describing three deaths in U.S. infants aged less than 12 months associated with cough and cold medications.[13] As a result of these deaths, the CDC is collaborating with DNCE and the Division of Drug Risk Evaluation (DDRE) to review adverse event reports submitted to the Agency through the MedWatch program regarding the use of decongestants and antihistamines in children.

Over-the-counter (OTC) and prescription cough and cold medicines containing decongestants and antihistamines are prescribed widely by general pediatricians to offer relief from the symptoms of the common cold.[14] More than 800 cough/cold preparations, including pediatric preparations, are available in the United States.[15] Although they are generally safe and well tolerated in the adult population, there is limited data in children less than 2 years of age with regard to efficacy and safety of cough and cold medications. Cough and cold preparations are among the most common substance category involved in pediatric exposures as reported to the poison control centers. Data from the 2004 annual report of the American Association of Poison Control Centers indicate that of the 1,250,536 poison exposures in children younger than 6 years of age, 67,494 (5.4%) were exposures to cough and cold preparations (accidental and non-accidental).[16]

Several articles regarding the safety and efficacy of over-the-counter cough and cold medicines in children have been published.[17,18,19] In March of 2006, the Division of Pulmonary and Allergy Drug Products (DPADP) released a Health Hazard Evaluation (HHE) regarding the use of cough and cold products containing carbinoxamine maleate and pseudoephedrine hydrochloride (PSE) with or without dextromethorphan, in patients less than 1 year of age.[20] As a result of the HHE, a Federal Registry notice (effective as of

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[13] Centers for Disease Control and Prevention. 2007. Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005. *M.M.W.R.* 56 (01);1-4.

[14] Carr BC. Efficacy, abuse, and toxicity of over-the-counter cough and cold medicines in the pediatric population. Curr Opin Pediatr . 2006;18:184-188.

[15] Kelly LF. Pediatric cough and cold preparations. Pediatrics in Review. 2004;25(4):115-23.

[16] Watson WA, Litovitz TL, Rodgers Jr. GC, Klein-Schwartz W, Reid N, Youniss J, Flanagan A, Wruk KM. 2004 annual report of the american association of poison control centers toxic exposure surveillance system. American Journal of Emergency Medicine. 2005;23(5):589-666.

[17] Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications - postmortem findings in infants and the relationship to cause of death. Journal of Analytical Toxicology. 2005;29(7):738-43.

[18] Bhatt-Mehta V. Over-the-counter cough and cold medicines: Should parents be using them for their children? Annals of Pharmacotherapy. 2004;38(11):1964-6.

[19] Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of over-the-counter cough and cold medications. Pediatrics. 2001;108(3).

[20] DPADP Review: Starke P. Health Hazard Evaluation Consult for cough/cold products containing carbinoxamine maleate and pseudoephedrine hydrochloride. March 3, 2006.

June 9, 2006), announced the removal of all unapproved drug products containing carbinoxamine from the market and revised the labeling to indicate use only in 2 years and above.

Pseudoephedrine, phenylephrine, and ephedrine are nasal decongestant drug products listed in the OTC monograph. The OTC dosing recommendations for decongestants start at age 2 years and above, with the statement to "consult a physician" for dosing recommendations below 2 years of age. Pseudoephedrine is more commonly found in cough and cold preparations than phenylephrine, although its notoriety as a methamphetamine precursor has led some governments to restrict its sale. The Combat Methamphetamine Epidemic Act (CMEA) of 2005 was signed into Law on March 9, 2006 to regulate, among other things, retail over-the-counter sales of ephedrine and pseudoephedrine products.[21] Retail provisions of the CMEA include placement of the product out of direct consumer access, daily sales limits, monthly purchase limits, and maintenance of sales logbooks.

Brompheniramine, chlorpheniramine, and diphenhydramine are antihistamine drug products listed in the OTC monograph. The OTC dosing recommendations for antihistamines start at age 6 years and above, with the statement to "consult a physician" for dosing recommendations below 6 years of age. In small children, there is no evidence that antihistamines have any benefit other than inducing sleep.[22]

In this consult we were asked to 1) analyze cases in children less than 6 years of age, 2) address whether the safety concerns were related to the prescription or OTC use of these products, and 3) assess whether the adverse events were as a result of single product use or use of multiple products containing the same ingredients.

3. DRUG INFORMATION/ LABELING [23]

3.1. Decongestants

Decongestants cause vasoconstriction of blood vessels in the nasal mucosa. These medications target α as well as β receptors, which explains their potential side effects, including tachycardia and hypertension.[24] Alpha-adrenergic agonists are used extensively as nasal decongestants in allergic rhinitis and in acute rhinitis in patients with upper respiratory infections.[25]

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[21] http://www.deadiversion.usdoj.gov. Accessed September 26, 2006.
[22] Kelly LF. Pediatric cough and cold preparations. Pediatrics in Review. 2004;25(4):115-23.
[23] CFR 21 Food and Drugs 341.80 Labeling of nasal decongestant drug products. pg 250-254. Revised as of April 1, 2006.
[24] Phenylpropanolamine (PPA) is a decongestant that was taken off the market in November 2006 because of its association with cardiomyopathy and intracranial hemorrhage.
[25] Goodman & Gilman's The Pharmacological Basis of Therapeutics - 11th Ed. (2006). Accessed online 9/18/2006.

Pseudoephedrine (PSE) hydrochloride is a stereoisomer of ephedrine that is less potent than ephedrine in producing tachycardia, increased blood pressure, and CNS stimulation. PSE and phenylephrine are α- and, to a lesser extent, β-adrenergic receptor agonists. Because of the predominant α–adrenergic properties on the arterioles that supply the nasal mucosa, they are used primarily as nasal decongestants. Pseudoephedrine and phenylephrine are found in many OTC preparations either as single-ingredient preparations, or more commonly in combination with antihistamines, acetaminophen and/or ibuprofen.

Adverse reactions for nasal decongestants as stated in the OTC monograph Warnings section labeled for children less than 12 years of age include:

- Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor.
- If symptoms do not improve within 7 days or are accompanied by fever, 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.
- **Pseudoephedrine** (oral nasal decongestant) - Children 6 years to under 12 years of age: 30 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 2 to under 6 years of age: 15mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children under 2 years of age: consult a doctor.
- **Phenylephrine** (oral nasal decongestant) - Children 6 years to under 12 years of age: 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years of age: 2.5mg every 4 to 6 hours not to exceed 15 mg in 24 hours. Children under 2 years of age: consult a doctor.
- **Ephedrine** (nasal drops) - Children 6 years to under 12 years of age: 1 or 2 drops or sprays in each nostril not more often than every 4 hours. Children under 6 years of age: consult a doctor.

3.2. Antihistamines

The first-generation antihistamines block H1 receptors on nasal vasculature and compete with histamine for receptor sites. They can also cross the blood-brain barrier and affect the central nervous system (CNS).[26] Diphenhydramine, brompheniramine and chlorpheniramine are H1 antagonists available in numerous over-the-counter preparations. The drying action of the mucous membranes is due to the anticholinergic properties of the first-generation antihistamines. Diphenhydramine often used for its sedative effects in adults, can cause paradoxical central nervous system stimulation in children, with effects ranging from excitation to seizures and death.

Adverse reactions for antihistamines as stated in the OTC monograph Warnings section labeled for children less than 12 years of age include:

[26] Kelly LF. Pediatric cough and cold preparations. Pediatrics in Review. 2004;25(4):115-23.

- 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.
- **Brompheniramine/chlorpheniramine** – May cause drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do no give this product to children who are taking sedatives or tranquilizers, without first consulting the child's doctor.
- **Diphenhydramine**
    - May cause marked drowsiness. Sedatives and tranquilizers may increase the drowsiness effect. Do no give this product to children who are taking sedatives or tranquilizers without first consulting the child's doctor.
    - Do not use with any other product containing diphenhydramine, even one used on skin.
- **Brompheniramine** maleate (oral) - Children 6 years to under 12 years of age: oral dosage is 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.
- **Chlorpheniramine** maleate (oral) - Children 6 years to under 12 years of age: oral dosage is 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.
- **Diphenhydramine** hydrochloride (oral) - Children 6 years to under 12 years of age: oral dosage is 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

4. DECONGESTANTS

4.1. Pseudoephedrine

4.1.1. Selection of case series

On September 13, 2006, the AERS database was searched using the ingredient name pseudoephedrine, for all cases of pediatric fatalities for children aged six years and under. The cases were limited to U.S. domestic cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The search yielded 95 raw count reports. The cases were individually reviewed and duplicates were consolidated. Of the 95 raw cases, 28 cases were duplicates and 21 additional cases were excluded for the following reasons:

- Foreign reports (2)
- Homicide unrelated to pseudoephedrine use (4)
- Report withdrawn as being unrelated to pseudoephedrine by attorney (1)
- Adverse event not clearly identified in the report (1)
- Reports were associated with Infant Tylenol drops (6)
- Report associated with litigation of Phenylpropanolamine containing products (1)
- Reports were associated with unspecified Tylenol products without evidence of pseudoephedrine as a contributory product (6)

4.1.2. Summary of Cases

An AERS search conducted on September 13, 2006 for reports of pediatric fatalities associated with pseudoephedrine use retrieved 46 unique domestic spontaneous cases. The cases that are included in this analysis are summarized in the table below and a line-listing of the cases are presented in Appendix I:

Table 1. Summary of Demographics and Characteristics of AERS Pseudoephedrine Pediatric Fatal Cases received between 4/1/1975 and 9/13/2006 (N=46)		
Sex		
	Male	23
	Female	19
	Unknown	4
Age		
	0 – 2 months	12
	3 – 12 months	25
	12 – 24 months	4
	36 – 72 months	5
	Median = 4 months	
	Range = 1 – 48 months	
Indication		
	Viral tracheitis – 1	Congestion – 4
	Bronchial infection – 1	Cough – 2
	Bronchiolitis – 2	Fever – 2
	Cold – 6	Flu – 3
	Nasopharyngitis – 1	URI – 6
	Otitis media – 1	Allergy – 1
	Teething/rhinorrhea – 1	Unknown – 15
Dose		
	3 mg – 1	25 mg – 2
	3.75 mg – 1	30 mg – 1
	6 mg – 1	37.5 mg – 1
	6.25 mg – 4	93.75 mg – 1
	15 mg – 5	Unknown – 30
Time to onset		
	1 dose – 5	3 days – 3
	2 doses – 3	5 days – 1
	3 doses – 1	31 days – 1*
	1 day – 6	Unknown – 24
	2 days – 3	
Product Classification†		
	OTC	16
	Rx	23
	Unknown	7
Reported Drug Name (n=37) ‡		

Table 1. Summary of Demographics and Characteristics of AERS Pseudoephedrine Pediatric Fatal Cases received between 4/1/1975 and 9/13/2006 (N=46)		
	Actifed Syrup – 1	Infant's Tylenol Plus Cold – 3
	Actifed-C – 1	Novahistine DH liquid – 1
	Benadryl Allergy/Sinus – 1	Pediacare cough/cold liquid** – 1
	Benadryl decongestant Liquid** – 1	Robitussin Pediatric Night – 1
	Carbaxefed DM RF – 2	Rondec** – 3
	Cardec DM ** – 1	Rondec oral drops – 6
	Cardec DM drops – 4	Rondec DM oral drops – 3
	Cardec DM syrup – 1	Sudafed – 1
	Dimetane DX – 1	Triaminic Liquid Cough and Cold – 1
	Efidac – 1	Tussend – 1
	Infant's Pediacare Decongestant and Cough – 1	Vicks 44E Cough/Chest Congestion – 1
Concomitant Medications§ (N=18)		
	Septra – 1	Cod liver oil – 1
	Nystatin – 2	Metaproterenol – 1
	Antibiotic (unspecified) – 5	Theophylline – 1
	Acetaminophen – 4	Ceftin – 1
	Amoxicillin – 3	Cipro – 1
	Gentamicin – 2	Pediazole – 1
	Ampicillin – 2	Loperamide – 1
	Ibuprofen – 2	Ex-Lax – 1
Outcome		
	Death – 46	
Receive Year		
	1975 – 1	1997 – 1
	1980 – 1	2000 – 3
	1983 – 2	2001 – 2
	1988 – 1	2002 – 4
	1989 – 1	2003 – 4
	1991 – 2	2004 – 5
	1993 – 3	2005 – 5
	1995 – 2	2006 – 8
	1996 – 1	
Reporter Type		
	Healthcare Professional	32
	Consumer	10
	Unknown	4
Type of Report		
	15-Day	34
	Direct	8
	Periodic	4

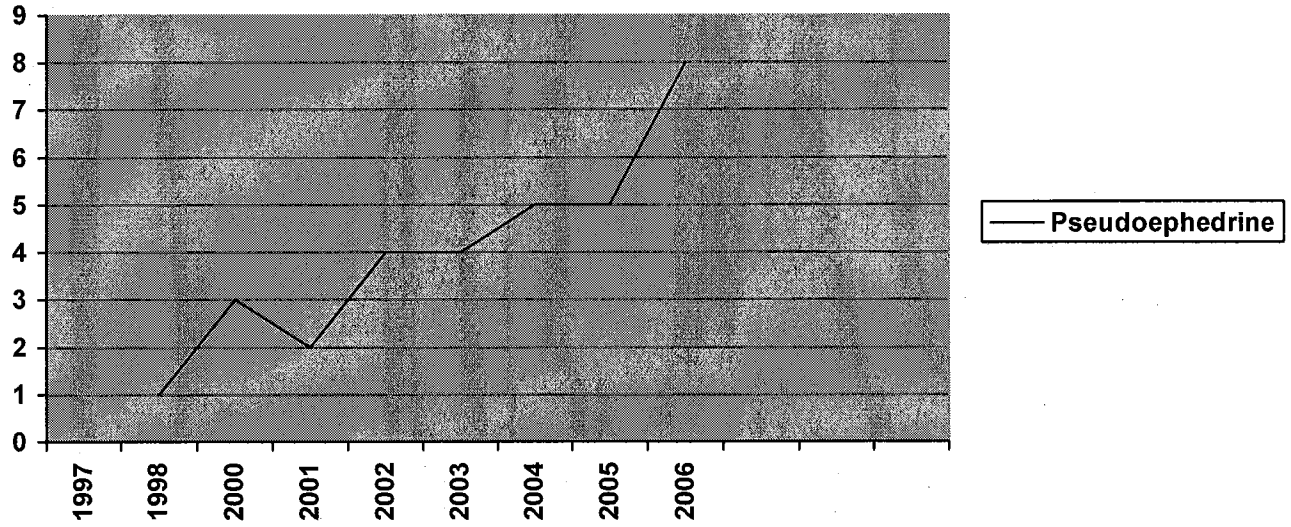
* Patient was on Benadryl Sinus on a regular basis for unspecified allergy symptoms
† Product classification was determined based on trade name or per report

‡ The drug name is the verbatim name provided by the reporter
** Unspecified formulation
§ These include concomitant medications other than cough and cold products

There were nearly equal numbers of female (19) and male (23) patients in this case series. The age range was 1 to 48 months, with a median age of four months. The majority of the reports occurred in children less than 1 year of age. Among the cases with a reported indication the majority were indicated for upper respiratory tract infections, to include cold, flu, bronchial infection, nasopharyngitis, etc. Four cases reported congestion as the indication and five cases reported cough (2), fever (2), and teething/ rhinorrhea (1) as the indication. One additional case reported allergy as the indication for use. In the remaining 15 cases, the indication was not provided.

The dose and time to onset were not well documented fields in the MedWatch reports. Based on the drug name and the milliliters reported, the pseudoephedrine dose was determined in a little over a third of the cases (17). Pseudoephedrine dose ranged from 3 mg to 94 mg, with a median of 15 mg. With the exception of one case, all 16 of 17 cases involved infants less than 2 years of age. The one case involved a 48 month old child who received the recommended dose of 15 mg every 4 to 6 hours. However, in this case the child was on multiple cough and cold products and may have received duplicate dosing. The time to onset was available for 23 of the reports, with 14 (61%) cases reporting an onset of less than 1 day; including fives cases that reported the use of a single dose. The actual product name was provided in 37 of the 46 cases. Of the 46 cases, 23 of the cases were associated with a prescription pseudoephedrine containing product (50%) and 16 were associated with OTC products; in the remaining seven cases it was unspecified. About 46 % of the pseudoephedrine cases with a reported trade name were associated with a non-approved prescription product (e.g. Rondec®, Cardec DM ®, Tussend®, etc.).

Figure 1. Number of AERS pseudoephedrine domestic cases of pediatric fatalities by year received (from 1997 to September 13, 2006)



These reports were received from 1975 to the present and the quality of the reports is highly variable. The event date was available in about half of the cases (n=25). From the cases that had a documented event date, seven of these occurred in the last 3 years. Since the event date field was not well documented, the received date was used to trend by year of occurrence. Based on the date of the reports received by the Agency, there seemed to be a slight increase in the number of reports of infant mortality associated with pseudoephedrine use. The majority of the cases were reported by healthcare providers (69%) and were submitted as expedited 15-day reports (74%). Of the 46 cases, 15 were literature reports submitted as 15-day expedited reports or periodic reports.

The reported adverse events in the cases were categorized according to the AERS system organ class (SOC) as shown below *(a report may contain more than one adverse event term)*:

Cardiac disorders [8]: Cardiac arrest (3), cardio-respiratory arrest (3), tachycardia (2)

Congenital, familial and genetic disorders [2]: Adrenal disorder (1), Arteriovenous malformation (1)

Ear and labyrinth disorders [1]: tympanic membrane (1)

Endocrine disorders [1]: diabetes insipidus (1)

Eye disorders [1]: eyes sunken (1)

Gastrointestinal disorders [4]: Constipation (2), vomiting (2)

General disorders and administration site conditions [19]: Condition aggravated (1), death (7), feeling cold (1), oedema (1), pharmaceutical product complaint (1), sudden infant death syndrome (6), hypothermia (1), listless (1)

Hepatobiliary disorders [2]: liver disorder (1), hepatic congestion (1)

Infections and infestations [10]: Bronchitis (2), Bronchitis acute (1), bronchopneumonia (1), pneumonia (4), meningitis (2)

Injury, poisoning and procedural complications [29]: Accident (1), Accidental exposure (2), Accidental overdose (2), drug toxicity (6), head injury (1), overdose (8), multiple drug overdose (1), medication error (7), therapeutic agent toxicity (1)

Investigations [17]: Bacteria urine identified (1), Blood chloride increased (1), Blood electrolytes abnormal (1), Blood glucose decreased (1), Blood potassium increased (1), blood sodium increased (1), blood urea increased (1), Drug level above therapeutic (3), drug screen positive (3), toxicologic test abnormal (3), laboratory test interference (1)

Metabolism and nutrition disorders [2]: dehydration (1), hyperglycemia (1)
Musculoskeletal and connective tissue disorders [2]: joint stiffness (2)

Nervous system disorders [20]: Apnea (3), cerebrovascular accident (1), Coma (9), Convulsion (1), depressed level of consciousness (1), headache (1), loss of consciousness (1), hydrocephalus (1), hyperaesthesia (1), lethargy (1)

Psychiatric disorders [6]: Agitation (1), Crying (1), hallucination (1), screaming (3)

Renal and urinary disorders [1]: renal failure (1)

Respiratory, thoracic and mediastinal disorders [13]: Bronchiolitis (1), Cyanosis (1), Dyspnoea (1), respiratory arrest (1), respiratory failure (2), pulmonary congestion (2), pulmonary oedema (2), lung disorder (1), rhinitis (1), hyperventilation (1)

Skin and subcutaneous tissue disorders [3]: urticaria (1), petechia (1), skin disorder (1)

Vascular disorders [3]: haemothorax (1), hemorrhage (1), hypertension (1)

A significant number of reports described either drug toxicity or overdose. Clinically significant events and notable groupings of reactions are discussed in more detail below (there were two cases that fell into more than one category).

Drug Toxicity/ Overdose (N=35)*

Thirty-five cases reported adverse event terms that related to overdose/drug toxicity. The preferred terms (PT) for these cases were coded as *drug toxicity, overdose, accidental overdose, multiple drug overdose, medication error, drug level above therapeutic, accidental exposure, drug screen positive, pharmaceutical product complaint, and toxicologic test abnormal.* These cases were analyzed for manner of overdose and were further grouped into the following categories: use of multiple cough and cold preparations, medication error, intentional overdose, accidental exposure, opiate intoxication, and undeterminable.

Of the 35 cases, nine cases reported the use of concomitant products. Seven cases reported the use of multiple cough and cold preparations. One case reported toxic levels of the anti-emetic metocloperamide in addition to the cold medications. Another case reported an infant consuming an OTC cough and cold product, a dose of loperamide and an unknown amount of sennosides (Ex-Lax). Of these nine cases, six cases reported above therapeutic levels of pseudoephedrine ranging from 1.4 mg/L to 29.9 mg/L; in the remaining three cases, pseudoephedrine blood levels were not reported. In seven of the nine cases, above therapeutic levels of the following cough and cold ingredients were detected postmortem: dextromethorphan, acetaminophen, chlorpheniramine, diphenhydramine, and brompheniramine.

* Two cases were included in both the overdose/drug toxicity and SIDS category

Medication error was reported as an adverse event in seven cases. Three additional cases were considered as a possible medication error upon further review, but were not coded as such. Five of these 10 cases were related to wrong dosage administration, 3 of which were administered by the parent/caregiver. The first case involved a 3-month old infant who received 2.5 ml of Sudafed syrup (15 mg of PSE) every 4 to 6 hours for 3 days instead of the prescribed 0.5 to 1 ml (3 - 6 mg of PSE) every 4 to 6 hours. The second case reported that a 4-month old infant received 3.75 ml (93.75 mg of PSE) of Cardec DM drops instead of the prescribed 0.75 ml (18.75 mg of PSE). The third case reported that the caregiver poured the medication directly from the bottle into the child's mouth.

The fourth case reported wrong dose being dispensed by the pharmacist, although cause of death was reported as SIDS. The fifth case reported the wrong dose being prescribed by the physician. In this case, a 2-month old infant was prescribed Rondec oral drops (1 dropperful every 6 hours as needed) for congestion. The infant expired on the same day with the cause of death reported as unknown. The medical examiner reported the pseudoephedrine level of 0.91 mg/L and carbinoxamine level of 0.12 mg/L. According to the report the "recommended" dose of Rondec oral drops for a 2-month old infant is ¼ dropperful or 6.25 mg of PSE every 6 hours.

In the remaining five cases involving a possible medication error, one case reported the cause of death to be toxic effects of pseudoephedrine due to possible duplicate dosing by multiple caregivers. A second case described a 2-month old that received a cough and cold medication intended for a 9-year old. In the third case, the child erroneously received a prescription cough and cold medication containing hydrocodone that was prescribed for the patient's father. The cause of death in this case was most likely related to opioid intoxication. Two additional cases were considered as medication errors by the reporter due to use of multiple products and were included in the discussion of the concomitant products.

Six additional were identified with the following manner of overdose: possible intentional overdose by caregiver (2), accidental exposure (1), overdose due to possible drug interaction or general inadequacies in dosage and administration of cough and cold preparations (1), and overdose likely related to opiate intoxication (2). In the remaining 12 cases there was insufficient information to determine the manner of overdose; however, 9 of the 12 cases reported postmortem pseudoephedrine concentrations that were above therapeutic level. The cause of death among the 12 cases was reported as acute intoxication (1), overdose (1), sudden death/bilateral pneumonia (1), apnea of prematurity (1), and unknown (8).

Sudden Infant Death Syndrome (N=7)*

Seven cases reported the cause of death as Sudden Infant Death Syndrome (SIDS) or "crib death". Majority of the cases (6) reported an event date prior to 2001. One case reported that a dispensing error was involved (included above); however, the autopsy indicated that the patient had died from a natural cause, which was thought to be SIDS.

* Two cases were included in both the overdose/drug toxicity and SIDS category

Another case also reported overdose as an adverse event due to either a possible drug interaction between Rondec® oral drops and theophylline or due to the general inadequacies in dosage and administration of cough and cold preparations; however, the cause of death was reported as SIDS by the family physician.

Among the seven cases with SIDS reported as an adverse event, only one case reported a postmortem pseudoephedrine level. The level was reported as 2.9 mg/L and intoxication by overdose with the OTC cold medication was suspected. In the remaining four cases there was insufficient information to determine the cause of death or an association with pseudoephedrine use. However, in all four cases a time to onset was reported as 1 dose to 1.5 days of using a cough and cold preparation containing pseudoephedrine. Therefore, the contributory role of pseudoephedrine could not be excluded in these cases.

Cardiac Arrest (N=2)

Two cases reported the cause of death as cardiac arrest. The first case reported a 2-month with a history of bronchitis and DPT and OPV vaccinations four days prior to event, died of cardio-respiratory arrest with etiology unknown. Further history reveals that the infant had been on Rondec® ¼ teaspoonful (frequency unknown). The Rondec® formulation in this case was unknown and no toxicology results were reported.

The second case reported an 18 month old infant receiving concentrated Infants' Tylenol Cold Plus for the treatment of a fever as recommended by the pharmacist. No concomitant medications were reported. Five minutes after taking the medication the infant had a seizure, developed hives and became limp. The infant had no history of epilepsy or febrile seizure. The infant was taken to the emergency room where his heart stopped. The father reported that his son had taken the exact same product before without any problems. Examination of the product did not reveal any evidence of product tampering or quality problems. Field sample analysis results indicated the presence of acetaminophen, dextromethorphan, and pseudoephedrine. No other information was provided.

Miscellaneous (N=4)

Of the 46 cases, the adverse event or cause of death was difficult to determine in four of the cases. The first case reported that the infant died on day 16 of hospitalization and the physician was unsure if the child had meningitis or trauma to the head. The second case reported that a 3-month old premature infant with a history of congestion and a viral infection one month prior to death, died within 12 hours of receiving immunization (unspecified). The infant was administered 2 dropperfuls of a pediatric infant Tylenol cough and cold preparation to ease possible fever or pain from the immunization. The autopsy results and cause of death were unknown. The third case reported that a 2-month old died in his sleep. According to the mother, the infant had bronchial pneumonia and had been misdiagnosed. The mother was inquiring whether the Rondec® drops that had been prescribed by the physician could have agitated the child's underlying disease. The fourth case reported that a 5-month old infant had received Pediacare decongestant cough

and cold on three different nights starting in December 2003. The night of 1/6/04 the child was crying and the following morning the patient was deceased. No other information was provided.

4.1.3. Pseudoephedrine Blood Levels

Of the 46 cases, 24 cases reported postmortem pseudoephedrine blood levels. The postmortem pseudoephedrine levels ranged from 0.67 mg/L to 31 mg/L, with a median of 3.8 mg/L. Pseudoephedrine therapeutic plasma concentrations range between 0.05 - 0.7 mg/L.[27] Data compiled from previously published scientific literature and from prior Office of the Chief Medical Examiner (OCME) experience report a therapeutic pseudoephedrine level of less than 1 mg/L and lethal levels of above 10.0 mg/L.[28] Of the 24 cases, most of them occurred in the 0 to 2 year old population group. Of the reports with a reported drug name, 11 were associated with the use of a prescription product, five with the use of an OTC product and in the remaining eight cases it is unknown which product was used.

Of the 24 cases with pseudoephedrine levels, 22 cases reported pseudoephedrine blood levels greater than the therapeutic level, of which eight were above the lethal level (Appendix I). The two cases that reported pseudoephedrine levels less than 1 mg/L were 0.91 mg/L and 0.67 mg/L in a two month old and four month old infants, respectively. Four cases reported pseudoephedrine as the only drug detected postmortem. However, in three of the cases the adverse event was associated with the use of multi-ingredient cough and cold products; therefore, it is possible that levels for other drugs were not tested. Of the 24 cases, six of the cases with an above therapeutic pseudoephedrine blood level reported the use of multiple cough and cold products.

4.2. Phenylephrine

4.2.1. Selection of case series

On September 13, 2006, the AERS database was searched using the ingredient name phenylephrine, for all cases of pediatric fatalities for children aged six years and under. The cases were limited to U.S. domestic cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The search yielded 16 raw count reports. The cases were individually reviewed and duplicates were consolidated. Of the 16 raw cases, four cases were duplicates. Eight additional cases were excluded for the following reasons: did not involve the use of phenylephrine (6); likely related to device failure during surgery (1); and likely related to another medication (1).

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[27] Regenthal R, Krueger M, Koeppel C, Preiss R. Drug levels: Therapeutic and toxic serum/plasma concentrations of common drugs. Journal of Clinical Monitoring and Computing. 1999;15(7-8):529-44.
[28] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

4.2.2. Summary of Cases

An AERS search conducted on September 13, 2006 for reports of pediatric fatalities associated with phenylephrine use yielded four unique domestic spontaneous cases. A line-listing of the cases are presented in Appendix II.

Gender was reported in three of the four cases with one female and two males; gender was unspecified in one case. The age of the patients ranged from 1.5 months to 36 months, with the median of 12.5 months. Indication was reported as cough (1), cough & congestion (1), and unknown (2). Dose was available in only one case involving a 4 month old and was reported as 2.5 mg every 4-6 hours administered for 2 days. Two cases reported the use of Phenergan VC which contains codeine and is a prescription product. The remaining two cases involved OTC products. Most of these cases were highly confounded with underlying medical conditions or the use of other medications to include opiates. All four cases identified in the AERS database associated with phenylephrine use occurred prior to year 2004. Only one case reported overdose as an adverse event. This case was submitted by a lawyer in a homicide case and the manner of overdose was reported as a non-accidental. Given the limited number and clinical information of the cases, the association between the adverse events reported in these cases and the use of phenylephrine was unclear.

4.2.3. Phenylephrine Blood Levels

Postmortem phenylephrine levels were not reported in these cases. Furthermore, we did not identify published literature or reports from the OCME that provided therapeutic or toxic postmortem phenylephrine levels.

4.3. Ephedrine

4.3.1. Selection of case series

On September 13, 2006, the AERS database was searched using the ingredient name ephedrine, for all cases of pediatric fatalities for children aged six years and under. The cases were limited to U.S. domestic cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The search yielded 10 raw count reports. The cases were individually reviewed and duplicates were consolidated. Of the 10 raw cases, five cases were duplicates and one additional case was excluded since the adverse reaction was related to improper administration and management of anesthesia.

4.3.2. Summary of Cases

An AERS search conducted on September 13, 2006 for reports of pediatric fatalities associated with ephedrine use yielded four unique domestic spontaneous cases. A line-listing of the cases are presented in Appendix III.

Gender was reported in three of the four cases with two males and one female; gender was unspecified in one case. The age of the patients ranged from 2 months to 5 months. The indication was reports as cold like symptoms (2), congestion (1), and unknown (1). Dextromethorphan was considered as a co-suspect drug in three of the cases and pseudoephedrine in four of the cases. There was no specific trade name or doses provided with these cases. All four cases were literature reports described in the Journal of Analytical Toxicology, 2005 and were also captured in the pseudoephedrine case series (section **4.1.2**).

Three of the four cases were coded for the adverse event term '*drug toxicity*' and the fourth case was coded for the adverse event term '*drug screen positive*'. Two of the cases reported multiple drug intoxication as the cause of death. The third case reported the cause of death as SIDS; however, according to the report the physician suspected drug intoxication. In the fourth case the cause of death was unknown.

4.3.3. Ephedrine Blood Levels

Postmortem ephedrine levels were reported as 0.50 mg/L, 0.10 mg/L, 0.09 mg/L, and 0.12 mg/L in the four cases. Ephedrine therapeutic plasma concentrations range between 0.1 - 0.6 mg/L, with lethal levels above 5 mg/L.[29] In all four cases, other cough and cold medications to include pseudoephedrine, dextromethorphan, acetaminophen, and carbinoxamine were also detected postmortem.

5. ANTIHISTAMINES

5.1. Diphenhydramine

5.1.1. Selection of case series

On September 13, 2006, the AERS database was searched using the ingredient name diphenhydramine, for all cases of pediatric fatalities for children aged six years and under. The cases were limited to U.S. domestic cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The search yielded 58 raw count reports. The cases were individually reviewed and duplicates were consolidated. There were 21 duplicates and four additional cases were excluded for the following reason: did not involve the use of diphenhydramine (1), report not involving a pediatric patient (2), and report associated with strangulation (1).

5.1.2. Summary of Cases

An AERS search conducted on September 13, 2006 for reports of pediatric fatalities associated with diphenhydramine use yielded 33 unique domestic spontaneous cases. A line-listing of the cases are presented in Appendix IV.

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[29] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

There were slightly more male patients (17) than female (14); gender was not specified in two of the cases. The age of the patients ranged from 1.5 month to 72 months, with a median age of 6 months. Indication was reported as allergy (1), sleep problem (3), intentional overdose (3), cough (1), rash (2), malaise (1), runny nose (1), accidental exposure (1), and unknown (20). Majority of the cases did not specify the product trade name or formulation, the dose, or time to onset. Therefore, for the diphenhydramine cases we are unable to discern between prescription and OTC diphenhydramine products. The majority of the cases were expedited reports (97%) received between 1971 and 2006. No specific trend can be appreciated from these cases. Of the 33 cases, 12 were consumer reports, 19 were reports by healthcare professional of which 14 were literature reports, and two were unknown. As with consumer reports and some literature sources, there was minimal amount of clinical data provided for each of the cases.

Thirty cases described adverse events related to overdose or drug toxicity. The preferred terms (PT) for these cases were coded as *drug toxicity, overdose, accidental overdose, multiple drug overdose, accidental exposure, drug level increased, intentional overdose, drug level above therapeutic, therapeutic agent toxicity, toxicologic test abnormal,* and *victim of homicide*. These cases were analyzed for manner of overdose and were further grouped into the following categories: intentional overdose, accidental exposure, multiple drug overdose, and undeterminable. Of the 30 cases, 11 cases were reported as intentional overdoses to include eight cases implicating homicide and/or criminal investigation. Some of these non-accidental cases involved the use of diphenhydramine for sedation administered by parents, babysitters or daycare providers. Six other cases were related to accidental exposure and three were likely related to multiple drug overdose. Of the three cases with reported multiple drug overdose, two cases mentioned the used of multiple cough and cold products and one case reported fatal levels of Periactin. In 10 additional cases the manner of overdose was unspecified; to include one case with the cause of death reported as SIDS.

In the remaining three cases, one case described an infant with an acute febrile illness who was administered 1 tsp Benadryl Elixir for respiratory distress which worsened 20 minutes later and the infant died. A second case reported the immediate cause of death as cardiorespiratory arrest and septic shock and varicella as the underlying causes. The third case reported that the fatal event was not considered drug related and no other information was provided.

5.1.3. Diphenhydramine Blood Levels

Of the 33 cases, 20 cases reported an actual postmortem diphenhydramine levels which ranged from 0.068 mg/L to 12.8 mg/L, with a median of 1.1 mg/L. Diphenhydramine therapeutic plasma concentrations range between 0.1 – 1 mg/L, with toxic levels above 2 mg/L and lethal levels above 8 mg/L; of note, significant postmortem diphenhydramine redistribution can occur. [30] Six additional cases reported the detection of diphenhydramine without actual levels specified; four were reported to be high or

[30] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

exceptionally high. Of the 20 cases with postmortem diphenhydramine levels, one case reported an actual dose and frequency. The case involved a 2-month old infant who was administered 0.8 ml of an oral Benadryl (formulation unspecified) once nightly as a sleep aid as recommended by the infant's physician. After two weeks of product use the infant expired. A toxicology report indicated diphenhydramine blood levels of 2.3 mg/L.

5.2. Brompheniramine

5.2.1. Selection of case series

On September 13, 2006, the AERS database was searched using the ingredient name brompheniramine, for all cases of pediatric fatalities for children aged six years and under. The cases were limited to U.S. domestic cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The search yielded 16 raw count reports. The cases were individually reviewed and duplicates were consolidated. There were three duplicates and four additional cases were excluded for the following reason: did not involve the use of brompheniramine (1), report associated with litigation of phenylpropanolamine containing products (1), adverse event likely related to another medication (1), and adverse event not clearly identified in the report (1).

5.2.2. Summary of Cases

An AERS search conducted on September 13, 2006 for reports of pediatric fatalities associated with brompheniramine use yielded 9 unique domestic spontaneous cases. A line-listing of the cases are presented in Appendix V.

There were four males and two females in this case series; gender was not specified in three cases. The age of the patients ranged from 1 month to 36 months, with a median age of 5 months. The majority of the cases did not specify a dose and time to onset was reported 1-dose (1), 2-days (1), 3-days (1), and 7-days (1). Indication was reported as upper respiratory tract infection (4), cough (1), and unknown (4). Six of the nine cases reported Dimetapp (4) or Dimetane DX (2) as the suspect trade names. Of the nine cases, four cases were associated with cough and cold preparations also containing pseudoephedrine and four cases were associated with products containing phenylephrine (captured in section **4.1.2 & 4.2.2)**. Of the nine cases, three of the cases were associated with a prescription brompheniramine containing product, five were associated with OTC products, and in one case it was unknown. There were no AERS reports identified in the AERS database after year 2004 of infant mortality associated with brompheniramine.

Five of these cases described overdose or drug toxicity as an adverse event. Three were most likely related to accidental overdose, one intentional, and one a homicide. The three cases that described events arising from an accidental overdose were associated with the use of multiple cough and cold products (1), accidental pediatric exposure (1), and possible medication error/negligence (1). Of the remaining four cases, three cases contained limited information and the cause of death was reported as SIDS (1), apnea (1),

and unknown (1). The fourth case reported fulminant hepatitis after receiving one dose of amoxicillin, lincomycin, and Dimetapp for a flu-like illness. The patient died after a liver transplant. The cause of death was unspecified and no other information was provided. The fifth case described an infant who was born premature who experienced cardiorespiratory arrest. The cause of death was reported as viral pneumonia after receiving Dimetane DX for two days.

5.2.3. Brompheniramine Blood Levels

Postmortem brompheniramine postmortem blood levels in the three cases were 0.4 mg/L, 0.19 mg/L, and 0.86 mg/L, respectively. Brompheniramine therapeutic plasma concentrations range between 0.005 - 0.015 mg/L.[31] A review of the Registry data suggest the postmortem brompheniramine concentrations of 0.4 mg/L and greater in children is indicative of brompheniramine poisoning.[32] In all three cases other cough and cold medications to include pseudoephedrine, dextromethorphan, and chlorpheniramine were also detected postmortem.

5.3. Chlorpheniramine

5.3.1. Selection of case series

On September 13, 2006, the AERS database was searched using the ingredient name chlorpheniramine, for all cases of pediatric fatalities for children aged six years and under. The cases were limited to U.S. domestic cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The search yielded 59 raw count reports. The cases were individually reviewed and duplicates were consolidated.

5.3.2. Summary of Cases

An AERS search conducted on September 13, 2006 for reports of pediatric fatalities associated with chlorpheniramine use yielded 27 unique domestic spontaneous cases. A line-listing of the cases are presented in Appendix VI. Of the 59 raw cases, 14 cases were duplicates and 18 additional cases were excluded for the following reasons:

- Adverse event related to maternal exposure (1)
- Adverse event not clearly identified in the report (1)
- Report associated with litigation of phenylpropanolamine containing products (1)
- Reports not involving chlorpheniramine use. Report associated with use of Tagamet (1), Concentrated Infant's Tylenol Cough/Cold (1), Triaminic Infant Oral drops (8), [33] and Pennwalt's Tussionex (5)[34]

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[31] Regenthal R, Krueger M, Koeppel C, Preiss R. Drug levels: Therapeutic and toxic serum/plasma concentrations of common drugs. Journal of Clinical Monitoring and Computing. 1999;15(7-8):529-44.
[32] Jumbelis MI, Hanzlick R, Cohle S. Alkylamine antihistamine toxicity and review of pediatric toxicology registry of the National Association of Medical Examiners: Report 4: Alkylamines. American Journal of Forensic Medicine & Pathology. 1997;18(1):65-69.
[33] Triaminic Oral infant drops (Rx) manufactured by Sandoz contained pheniramine, pyrilamine, and phenylpropanolamine. This product was discontinued and Novartis, created in 1996 by the merger of the

The cases involved more males (20) than females (6). The age of the patients ranged from 1 month to 72 months, with the median of 24 months. Among the cases with a reported indication (n=16) half were indicated for upper respiratory tract infections. The remaining eight cases reported cough (3), congestions (2), sleep (1), accidental exposure (1), and therapeutic error (1) as the indications. Based on the drug name and the milliliters reported, the chlorpheniramine dose was determined in eight of the cases; the dose ranged from 0.4 mg to 12 mg, with a median of 4 mg. The time to onset was available for 13 of the reports, with nine cases reporting an onset of equal or less than 1 day. The actual product name was provided in 24 of the 27 cases. Of the 27 cases, 16 of the cases were associated with a prescription chlorpheniramine containing product (57%) and 8 were associated with an OTC product; in the remaining 3 cases product classification was unspecified. Nearly half of the cases (n=13) were associated with the use of combination products containing chlorpheniramine and an opioid (hydrocodone – 12; codeine – 1); of which nine mentioned the specific trade name, Tussionex PK. Of the 27 cases, most were expedited 15-Day reports (74%) received between 1975 and 2006. Of the 27 cases, 18 were reported by healthcare providers, six were consumer reports and three were from lawyers.

Twenty cases reported adverse events terms related to overdose or drug toxicity. The preferred terms (PT) for these cases were coded as *drug toxicity, overdose, accidental overdose, multiple drug overdose, medication error, drug level increased, intentional overdose, drug level above therapeutic,* and *therapeutic agent toxicity*. These cases were analyzed for manner of overdose and were further grouped into the following categories: Four cases were most likely related to intentional overdose, to include two cases of reported homicide. Sixteen cases described events arising from an accidental overdose to include, medication error (5), multiple drug intoxication (3), and accidental exposure (2). In the remaining five cases the manner of overdose was unknown.

The remaining seven cases reported adverse events other than overdose and drug toxicity. Three cases were associated with hydrocodone-chlorpheniramine combination products and reported apnea, brain oedema/bronchitis/ coma, and death as adverse events. The fourth case reported a 22-month old patient with a history of febrile seizures on phenobarbital prescribed Triaminic (an unspecified child's formulation) for a stuffy nose. The infant received 1-2 doses of and was found dead the next morning. The cause of death was reported as unknown. The fifth case reported the use of multiple cough and cold medications with the cause of death reported as subarachnoid hemorrhage. In the last two cases the reporters felt that the cause of death was not drug related.

5.3.3. Chlorpheniramine Blood Levels

Five cases involving intentional (2) and accidental overdose (3) reported postmortem chlorpheniramine levels. Postmortem chlorpheniramine blood levels were 0.07 mg/L, 0.07 mg/L, 0.4 mg/L, 0.16 mg/L, and < 0.25 mg/L, respectively. Chlorpheniramine

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Swiss companies Ciba-Geigy and Sandoz, currently markets the different OTC preparations of Triaminic products.

[34] Tussionex (Rx) marketed by Pennwalt under the NDA# 10-768 contains hyrocodone and phenyltoloxamine and was discontinued by the company in April 22, 1988.

therapeutic plasma concentrations range between 0.01 – 0.02 mg/L, with lethal levels above 0.5 mg/L.[35]

6. DISCUSSION

The AERS cases demonstrate that the administration of cough and cold medicines in children less than 2 years of age could lead to serious adverse events including death. Since there are no dosing recommendations as per the OTC monograph for children under the age of 2, most of these cases could be considered off-labeled use. The most common adverse event implicated with these cases was drug overdose or drug toxicity. The manner of overdose was found to be due to accidental overdoses as well as intentional overdoses. Accidental overdose of both prescription and OTC cough and cold products were related to multiple product use, medication error, uncertainty in dosing, accidental exposure, and other preventable mistakes. Other factors contributing to accidental overdose maybe as a result of drug interactions, or diseases that increase sensitivity to sympathomimetic and anticholinergic agents.

Medication error due to lack of proper dosage guidelines for the cough and cold products may be contributing to overdose in children less than 2 years of age. Parents and caregivers may not be aware of the duplication of ingredients and the potential risk of overdose when using multiple products. Furthermore, parents may be misinformed that OTC cough and cold medications intended for children 6 years and above are also safe in younger children and infants. Dosing suggestions for these products are often published by the manufacturers and are extrapolated from adult dosing. As in the case of the unapproved prescription product, Rondec®, the average recommended doses are age based and are provided as a range. Age based dosing may lead to increased risk of overdose, especially in infants who are below the average weight or are born premature. Furthermore, most cough and cold preparations are combinations of at least 2 or more ingredients, and it is unclear as to which active ingredient the dose is based on.[36] There is also the potential for confusion between the children's cough/cold products and the infants' concentrated drops (higher concentration) in regards to the dosing regimen that could lead to adverse events. Finally, some of the products are unapproved products (e.g. Rondec®, Cardec DM®, Tussend®, etc.) and the quality of these products is unknown. When manufacturers change the formulation of a product, new preparations of a particular cough and cold product should also be easily distinguished from existing preparation.

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[35] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

[36] Bhatt-Mehta V. Over-the-counter cough and cold medicines: Should parents be using them for their children? Annals of Pharmacotherapy. 2004;38(11):1964-6.

7. RECOMMENDATION

In conclusion, the AERS postmarketing data suggest that the use of prescription and OTC cough and cold medication in younger children, particularly in children less than 2 years of age, could result in fatal overdoses. Therefore, we recommend an educational campaign which addresses proper education about cough and cold products; in particular, the risks of using these products in children less than 2 years of age and the duplication of ingredients with the potential risk of overdose when using multiple products. In view of the current data that lacks the evidence of efficacy and the potential for toxicity, the labeling of cough and cold products (both prescription and OTC) should include prominent language to describe the risk of overdose in children. Also, we recommend that the current OTC dosing recommendation which suggests to "consult a physician" for decongestants in patients under 2 years of age and for antihistamines in patients under 6 years of age should be reconsidered. This statement is confusing and appears to contribute to medication errors which can result in fatal overdoses. We suggest that the revised wording state that dosing is not recommended in these age groups due to the lack of evidence of efficacy and safety concerns. Further, a timely forum among stakeholders is recommended to discuss making only single ingredient products available for pediatric formulations.

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Concur:

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Appendix I—Line Listing of AERS Pseudoephedrine Cases (N=46)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Pseudo-ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
3622919	1	M	11/29/00	*2000	Periodic (LIT)	HP	MA	Novahistine DH Liquid	Viral Tracheitis	2 doses		Acute opiate intoxication with contributory findings of severe bronchitis	The patient was born premature. Postmortem free codeine level: 0.34 mg/L.
4805237	2	F	10/17/05	*2005	15-Day	CS		Benadryl Allergy/Sinus	allergy		1.3 mg/L (HB)	Unknown	The patient was vomiting and was constipated two days prior to death. The patient had been on this medication on a regular basis. DPH postmortem level < 1 mg/L.
4883161	2	M	1/17/06	12/7/05	Direct	HP	IL	Carbaxefed DM/RF	interstitial pneumonia	2 doses	4.74 mg/L	Unknown	The patient did not have a bowel movement for four days prior to the event. Ibuprofen reported as suspect medication. Patient was also on an unspecified antibiotic.
1786939	2	F	7/9/96	2/16/95	15-Day	HP	OK	Cardec DM Drops	bronchial infection	1 day		Unknown	Per report PSE, CM, and DXM blood level was higher than therapeutic concentrations. Concomitant medications include Septra, Nystatin.
738234	2	M	4/5/91	10/5/90	15-Day	HP	WI	Cardec DM Syrup	URI	1 day		Possible SIDS	Details were not provided.
4789481	2	M	10/6/05	12/21/01	15-Day	CS	IN	Concentrated Infants' Tylenol Plus Cold	Fever/runny nose	1 day		Unknown	The patient died on day 16 of hospitalization. The physician was not sure if child had meningitis or trauma to the head.

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539964	2	M	8/21/88	*1987	Direct	HP	WI	Rondec	bronchitis			Cardiorespiratory arrest	The patient received immunization four days prior to event and had been on concomitant antibiotic therapy.
920794	2	F	2/2/93	9/11/92	15-Day	CS	OH	Rondec Oral Drops	nasal congestion	1 dose	0.91 mg/L (B)	Unknown	Medical examiner confirmed that prescription written for 1 dropperful q6h as needed. Recommended dose for a 2 month old is ¼ dropperful qid. CM level: 0.12 mg/L
1904582	2	M	3/20/97	*1997	15-Day	CS	OK	Rondec Oral Drops				Unknown	Patient with bronchial pneumonia. No details were provided.
3460252	2	M	2/22/00	1/25/99	15-Day	HP	PA	Rondec	cold	2 doses	17 mg/L (B)	Unknown	The mother had given the patient a dose of her 9 year olds' son Rondec (unspecified formulation). DXM level: 1.2 mg/L
4245164	2	F	11/28/03	*2003	15-Day (LIT)	HP			cold		14.4 mg/L (B)	Multiple drug intoxication	The patient was on multiple cough and cold medications. BPM blood level: 0.4 mg/L; DXM blood level: 0.5 mg/L
4986394	2	F	4/28/06	*2006	15-Day (LIT)	HP	OH		cold like symptoms	2 Days	2.2 mg/L (HB)	Acute intoxication with dextromethorphan, ephedrine, pseudoephedrine, carbinoxamine	Patient with no known health concerns.DXM blood level: 0.04 mg/L, ephedrine blood level: 0.50 mg/L, CM= 0.08 mg/L, APAP=16 mg/L.

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AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Pseudo-ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
68980	3	F	4/1/75	2/10/75	Periodic	HP	VA	Actifed-C	cough/ fever	5 days		Unknown	Possible overdose with codeine. "Given twice recommended dose" Codeine level of 12 mg/L.
738356	3	F	4/5/91	10/2/90	15-Day	HP	WI	Cardec DM Drops	cold/ congestion	1 day		Possible SIDS	Concurrent medications included APAP and an unspecified antibiotic.
4986084	3	F	4/28/06	*2006	15-Day (LIT)	HP	OH	Concentrated Infants' Tylenol Plus Cold		2 doses	0.52 mg/L (FB)	Unknown	The patient was 12 hour post immunization at time of event. APAP level of 1.7 mg/L and ephedrine level of 0.04 mg/L.
964471	3	M	5/10/93	4/2/93	15-Day	HP	TX	Rondec Oral Drops	URI	31 days	31 mg/L	Toxic effects of Pseudoephedrine	The patient may have received duplicate dose from multiple caregivers.
170036	3	M	10/14/83	9/7/83	15-Day		LA	Sudafed Syrup	URI	3 days		Unknown	The patient's mother administered 2.5 ml q4 – 6h for 3 days instead of the prescribed dose of 0.5 to 1.0 ml q4-6h. Per report, the patient had overwhelming sepsis. Concurrent medications included ampicillin, gentamicin and oxacillin.
4861466	3	F	12/20/05	10/5/03	Periodic (LIT)	HP	OH	Concentrated Tylenol Infants' Plus Cold Drops & Pedia Relief	Teething/ rhinorrhea	2 days	3.73 mg/L	death related to APAP	Patient on multiple cough and cold medications. APAP level of 64.3 mg/L. Apnea and cyanosis associated with an unrepaired cleft palate.

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4933382	3		3/1/06	*2006	15-Day (LIT)	HP	OH		cold like symptoms		2.9 mg/L (HB)	SIDS	Per report physician suspected intoxication by overdose. APAP level of 24 mg/L, ephedrine=0.09mg/L, levorphanol=0.04 mg/L and DXM=0.03 mg/L
4617455	4		3/22/05	*2005	15-Day	CS		Benadryl decongestant Liquid			3.3 mg/L (B)	Overdose	PPA level of 0.09 mg/L, DPH level of 0.8 mg/L. Both considered as co-suspect.
3948046	4	F	7/12/02	1/21/01	15-Day	HP	CA	Cardec DM Drops	congestion	3 doses	15 mg/L (HB)	Unknown	The father administered 3.75 ml instead of 0.75 ml that was prescribed. CM level of 1.7 mg/L, DXM level of 0.59 mg/L.
4199574	4		9/25/03	*2003	15-Day (LIT)	HP	NM	Efidac	flu-like symptoms		10 mg/L (HB)	Unknown	The caregiver poured medicine from the bottle directly into the infant's mouth. BPM level of 0.86 mg/L.
1672200	4	F	11/22/95	10/15/95	Direct	HP	FL	Rondec Oral Drops	Bronchio-litis	1.5 days		SIDS	No details provided.
602932	4	F	6/6/89	3/27/89	15-Day	HP	HI	Rondec Oral Drops	congestion	42 days	2.3 mg/L (B)	bilateral pneumonia/Sudden death	The patient was also on concurrent metaprterenol. CM level of 0.20 mg/L
4507106	4	F	11/18/04	*2004	15-Day (LIT)	HP	DC		intentional injury		16.2 mg/L (B)	cardiorespiratory arrest	The entire 15ml bottle was dispensed to the patient. The patient was also on concomitant antibiotic therapy.
4953867	4	M	3/21/06	*2006	15-Day (LIT)	HP					0.67 mg/L (HB)	Unknown	Ephedrine level of 0.12 mg/L

Appendix I—Line Listing of AERS Pseudoephedrine Cases (N=46)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Pseudo-ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
4286418	5	M	2/2/04	1/7/04	15-Day	CS		Infant's Pediacare Decongestant & Cough Drop	Flu	3 days		Unknown	No additional details were provided.
1615346	5	M	7/14/95	4/9/95	Direct	HP	GA	Rondec (unspecified formulation)			1.13 mg/L (B)	apnea of prematurity	The patient was born two months premature. Per reporter possible negligence due to high level of PSE.
4986101	5	M	4/28/06	*2006	15-Day (LIT)	HP	OH		congestion	1 dose	1.4 mg/L (CB)	Multiple drug intoxication	The patient was also on concomitant antibiotic therapy. Ephedrine level < 0.10 mg/L, CM 0.07 mg/L, APAP 6 mg/L, DXM 0.09 mg/L. and metocloperamide 0.67 mg/L.
4883158	6	F	1/17/06	12/15/05	Direct	HP	IL	Carbaxefed RF/Infant Tylenol Cold	Broncho-pneumonia	9 doses	6.8 mg/L	Unknown	Patient had ear infection and had recently received the flu shot. The patient was on multiple cough and cold medications and amoxicillin was considered a co-suspect medication. DXM level of 1.91 mg/L.
4013197	7	M	11/21/02	12/2/00	Direct	CS		Rondec DM Oral Drops	cold	1 dose		SIDS	The four month premature infant was supposed to receive1/2 dropper-full and the pharmacist wrote the directions as 1 ½ dropperful.
3486965	8	M	4/12/00	*2000	Direct	HP	TX	Cardec Drops/Cydek Drops	URI	1 day	3.8 mg/L (HB)	Unknown	Concomitant medications were amoxicillin and gentamicin. CM level of 0.43 mg/L.

Appendix I—Line Listing of AERS Pseudoephedrine Cases (N=46)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Pseudo-ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
170578	8	F	11/14/83	4/11/83	Direct		OH	Rondec	cold/ear infection			SIDS	Per report the adverse event was related to the synergistic reaction of Theophylline and Rondec. Patient was also on concurrent amoxicillin therapy.
4390491	9	M	6/30/04	12/9/03	15-Day	HP	FL	Rondec DM Oral Drops			3.4 mg/L	Unknown	CM level of 0.23 mg/L and DXM 0.058 mg/L.
3822323	9	M	11/7/01	*2001	15-Day (LIT)	HP	MD				10 mg/L (HB)	Multiple drug intoxication	The patient was given numerous doses of unspecified OTC cough and cold preparations. PPA level of 1.4 mg/L and DXM level of 0.6 mg/L.
112982	10	M	6/1/80	10/31/78	Periodic		WV	Actifed Syrup	URI	1 dose		Crib death	The patient had received on an unknown date DPT and polio vaccines.
3882397	11	M	3/14/02	11/16/01	Direct	HP	IL	Cardec DM	Cold	1 dose	1.5 mg/L	Unknown	CM level of 0.13mg/L and DXM level of 0.14mg/L.
4667930	18	M	5/20/05	4/6/05	15-Day	CS	AK	Concentrated Infants' Tylenol Plus Cold	fever	1 dose		Unknown	Per father, the patient had been on this product before.
1341985	24		6/21/93	*1993	15-Day	HP	MO	Dimetane DX				head trauma sustained in an alleged motor vehicle accident	The case is under criminal investigation. DXM level of 1.2 mg/L (B).

Appendix I—Line Listing of AERS Pseudoephedrine Cases (N=46)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Pseudo-ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
4477566	24	F	10/12/04	*2004	15-Day (LIT)	HP	DC				29.9 mg/L	Unknown	The patient was on multiple cough and cold medication. PPA level of 0.267 mg/L, DPH level of 5.25 mg/L.
4489215	24	F	10/28/04	*2004	15-Day (LIT)							Unknown	Vague report of fatal overdose from TESS annual report. Concomitant medications included DPH and PPA.
4206049	36	M	10/6/03	*2003	15-Day (LIT)	HP	DC	Pediacare Cough-Cold Liquid	URI	3 days	4.8 mg/L	Unintentional overdose/cardio respiratory arrest	An empty bottle of a cough and cold preparation was found. BPM level of 0.19 mg/L, DXM level of 0.009mg/L, CPM level of 0.04 mg/L.
3784128	48	F	8/28/01	1/2/00	15-Day	HP	DC	Vicks 44E Cough/Chest Congestion Relief Syrup/ Children's Tylenol Flu	flu-like symptoms			acute intoxication by oral ingestion of dextromethorphan	Patient on multiple cough and cold medication. DXM level of 0.61 mg/L
5013752	48	M	5/30/06	3/8/06	15-Day	CS		Robitussin Pediatric Night relief				Unknown	According to the patient's mother cause of death was considered overdose. Co-suspect medication included Imodium and Ex-Lax (sennosides) of which the child had consumed an unknown amount.

Appendix I —Line Listing of AERS Pseudoephedrine Cases (N=46)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Pseudo-ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
3975892	48	F	9/11/02	6/2/99	15-Day	CS	NJ	Triaminic Liquid cold & cough	otitis media/post nasal drip	16 days		subarachnoid hemorrage	The patient was on multiple cough and cold medications. Concurrent medications included Ceftin, Cipro, Augmentin, Pediazole, Tylenol and Zithromax.
4224863	48	M	11/3/03	*2003	15-Day (LIT)	HP	DC	Tussend	nasophary ngitis			cardiopulmonary arrest	The patient erroneously received hydrocodone that was prescribed for the father. Hydrocodone level of 0.67 mg/L and CPM level of 0.21 mg/L.

[a] CS=Consumer; HP=Health professional (i.e., pharmacist, nurse, MD, etc)
[b] HB=Heart Blood; FB= Femoral Blood; LB=Liver Blood; CB=Cavity Blood
[c] PSE=pseudoephedrine; DPH=diphenhydramine; DXM=dextromethorphan; CM=carbinoxamine; BPM=brompheniramine; CPM=chlorpheniramine; APAP=acetaminophen; PPA=phenylpropanolamine
* Date received by the manufacturer

Appendix II—Line Listing of AERS Phenylephrine Cases (N=4)												
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Cause of Death**	**Description**
1385811	1.5		11/9/93	*1993	15-Day	HP	TX	Entex Liquid			Unknown	The patient was brought to the emergency room and died shortly thereafter. The diagnosis was pneumonia. The infant was also on concomitant Dimetapp, Pediazole, and Ventolin syrup.
796664	4	M	12/5/91	11/1/90	15-Day	HP	AZ	Phenergan VC	Cough and congestion	2 days	SIDS	Autopsy revealed viral pneumonia and possible SIDS. The patient was born prematurely with diagnosis of "transient Tachypnea of the Newborn".
4911620	21	F	2/10/06	2/1/04	15-Day	LYR	CA	Phenergan VC	Cough	43 days	Unknown	The patient died after receiving last dose of Phenergan VC.
4265885	36	M	1/7/04	*2003	15-Day	LYR	CT	Dimetapp			Overdose	The attorney reported that the child had been forcefully administered Dimetapp and unspecified formulation of Triaminic liquid with malicious intent.

[a] CS=Consumer; HP=Health professional (i.e., pharmacist, nurse, MD, etc); LYR=Lawyer
* Date received by manufacturer

Appendix III—Line Listing of AERS Ephedrine Cases (N=4)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Ephedrine level (mg/L)[b]**	**Cause of Death**	**Description [c]**
4986394	2	F	4/28/06	*2006	15-Day (LIT)	HP	OH		cold like symptoms	2 Days	0.5 mg/L	Acute intoxication with DXM, ephedrine, PSE, and CM	The patient had no known health concerns. PSE postmortem level: 2.2 mg/L, DXM level: 0.04 mg/L
4933382	3		3/1/06	*2006	15-Day (LIT)	HP	OH		cold like symptoms		0.09mg/L (HB)	Sudden infant Death Syndrome	Per report physician suspected intoxication by overdose. APAP 24 mg/L, PSE 2.9 mg/L, DXM level of 0.03 mg/L, and levorphanol 0.04 mg/L
4953867	4	M	3/21/06	*2006	15-Day (LIT)	HP					0.12 mg/L (HB)	Unknown	PSE level of 0.67 mg/L
4933393	5	M	3/1/06	*2006	15-Day (LIT)	HP	OH		congestion	1 dose	< 0.10 mg/L (CB)	Multiple drug intoxication	The patient was also on concomitant antibiotic therapy. PSE level 1.4 mg/L, CM 0.07 mg/L, APAP 6 mg/L,DXM 0.09 mg/L, and metocloperamide 0.67 mg/L.

[a] CS=Consumer; HP=Health professional (i.e., pharmacist, nurse, MD, etc)
[b] HB=Heart Blood; CB=Cavity Blood
[c] PSE=pseudoephedrine; DPH=diphenhydramine; DXM=dextromethorphan; CM=carbinoxamine; BPM=brompheniramine; CPM=chlorpheniramine; APAP=acetaminophen; PPA=phenylpropanolamine
* Date received by manufacturer

Appendix IV—Line Listing of AERS Diphenhydramine Cases (N=33)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Diphenhydramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4146597	1.5	F	7/9/03	*2003	15-Day	HP (LIT)		Diphenhydramine			1.6 mg/L	Diphenhydramine intoxication	No additional details provided.
4805237	2	F	10/17/05	1/1/05	15-Day	CS		Benadryl Allergy/Sinus	Allergy		< 1.0 mg/L (HB)	Unknown	The patient was vomiting and was constipated two days prior to death. The patient had been on this medication on a regular basis. PSE postmortem level: 1.3 mg/L
4224919	2	F	10/31/03	*2003	15-Day	HP		Diphenhydramine			1.5 mg/L (HB)	Diphenhydramine intoxication	The patient had a history of "slight cold"
3814394	2	M	10/23/01	*2001	15-Day	HP (LIT)		Diphenhydramine			1.6 mg/L (HB)	Fatal overdose due to intentional misuse	The patient was brought to the ER in cardiorespiratory arrest.
4557454	2	M	1/18/05	*2005	15-Day	HP	MO	Benadryl	Sleep Problem	2 weeks	2.3 mg/L	Unknown	The patient was given 0.8ml of Benadryl for sleep as recommended by the physician.
3850833	2	M	1/9/02	7/31/01	15-Day	CS		Benadryl			detected	Unknown	Periactin was considered as co-suspect medication, with levels sufficient enough to have caused death.
4227012	2.5	M	11/4/03	*2003	15-Day	CS		Diphenhydramine			detected		A consumer reported that her 10 week old son "was murdered at his daycare center".
4867091	3	F	12/22/05	*2005	15-Day	HP (LIT)	OH	Diphenhydramine			0.14 mg/L	Compressional Asphyxia	Co-suspect Lorazepam
4325542	3	F	3/24/04	12/18/01	15-Day	HP		Benadryl	Intentional Overdose		1.0 mg/L	Diphenhydramine intoxication	The patient had been given more than 12 teaspoons of Benadryl allergy by a babysitter to quiet the child.

Appendix IV—Line Listing of AERS Diphenhydramine Cases (N=33)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Diphenhydramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4299304	3	F	2/17/04	*2004	15-Day	HP (LIT)	MD	Diphenhydramine			1.1 mg/L	Homicide by daycare	The daycare center owner had administered DPH to the patient.
4336975	3	M	4/8/04	*2003	15-Day	HP (LIT)	MN	Diphenhydramine	Intentional Overdose		1.1 mg/L	Diphenhydramine intoxication	The case remains under investigation.
4483968	3	M	10/21/04	2003	15-Day	LIT		Hydramine Elixir			6 mg/L (HB)	Unknown	The patient could not be resuscitated after his afternoon nap at a daycare facility.
4223262	3	M	10/28/03	5/23/03	15-Day	HP	IA	Benadryl	Malaise	1 day	High levels detected	Unknown	Investigators found high levels of Benadryl in the child's system. Tylenol (unspecified formulation) was also a co-suspect medication.
5114130	4	M	9/21/06	2/9/05	15-Day	CS		Benadryl	Coughing		0.8 mg/L	Diphenhydramine intoxication	Dimetapp was also considered a co-suspect medication. PSE level of 3.3 mg/L, PPA 0.09 mg/L
3802488	5	F	10/1/01	7/18/01	15-Day	LYR	NC	Benadryl			0.14 mg/L	SIDS	The patient died in the care of an unlicensed daycare provider. The attorney feels that the DPH was an adjunct in the death of the child.
34060	6	M	4/1/71	6/9/70	Periodic		MI	Benadryl	Rash			Unknown	Per report not considered drug related.
3966313	6	M	8/21/02	*2002	15-Day	HP(LIT)	TX	Diphenhydramine	Rash			Cardiorespiratory arrest and septic shock	The patient was admitted to the hospital after six days of varicella infection.
4236467	10	M	11/14/03	*2003	15-Day	CS		Tylenol			High levels detected	Multiple drug intoxication	High levels of DXM, CPM, DPH and metocloperamide were detected.

Appendix IV—Line Listing of AERS Diphenhydramine Cases (N=33)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Diphenhydramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4093802	12	M	4/10/03	1/31/03	15-Day	CS	MT	Benadryl	Insomnia		High levels detected	Diphenhydramine intoxication	The patient was given an unspecified amount of Benadryl by his daycare provider. Manner of death was considered as homicide.
4190519	12		9/15/03	*2003	15-Day	HP	MI	Benadryl			0.068 mg/L	Unknown	No additional details were provided.
745690	15	M	5/15/91	7/15/89	15-Day	HP (LIT)	PA	Benadryl			1.0 mg/L	Diphenhydramine intoxication	The patient accidentally ingested Benadryl capsules.
3776028	17	F	8/13/01	8/24/00	15-Day	CS		Benadryl	Runny Nose		0.27 mg/L	Asphyxiation	According to the coroner the Benadryl was a factor in the child deaths as it sedated her.
4459801	22	M	9/23/04	*2004	15-Day	HP (LIT)	DC	Extra Strength Tylenol PM	Accidental Exposure		7.78 mg/L	Multi-organ failure	The patient was found unresponsive next to an empty bottle of APAP and DPH. APAP level of 138.3 mg/L
4495135	24	F	11/4/04	*2004	15-Day	HP (LIT)	DC	Diphenhydramine			5.25 mg/L	Unspecified	The patient was on multiple cough and cold medications. PPA 0.267 mg/L
324410	24	F	2/8/85	1/1/85	15-Day		NJ	Benadryl		1 dose		Acute febrile illness	1 tsp of Benadryl elixir was given by mother for respiratory distress.
1530843	24	F	12/5/94	*1994	15-Day	CS	AL	Benadryl				Intentionally fatal overdose	Media report of a mother administering Benadryl. The patient was terminally ill and a d a birth defect
3971520	24	M	9/3/02	*2002	15-Day	HP (LIT)	CA	Benadryl				Unspecified	The infant accidentally ingested 19 Benadryl 25 mg tablets

Appendix IV—Line Listing of AERS Diphenhydramine Cases (N=33)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Diphenhydramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4520615	30	F	12/3/04	1/1/03	15-Day	CS		Benadryl				Unspecified	The child accidentally ingested 30-35 children's Benadryl tablets
1625500	34	F	8/9/95	*1995	15-Day	HP (LIT)	TX	Benadryl			12.8 mg/L	Adult respiratory distress syndrome (ARDS)	The patient developed seizures and was hospitalized after a presumed acute lethal ingestion of DPH.
4600345	48	F	8/3/04	6/27/03	15-Day	CS	SC	Diphenhydramine	Insomnia		High levels detected		High concentration of Demerol and OTC drugs including APAP and DPH were detected postmortem.
4416270	48		3/4/05	*2002	15-Day	HP (LIT)	DC	Diphenhydramine			0.2 mg/L		Child was reported to have died after accidental exposure of DPH, methadone, and promethazine.
4781665	60	M	9/27/05	*2005	15-Day	HP (LIT)	DC	Diphenhydramine			10 mg/L	Unspecified	The child took an unspecified amount of DPH. He was found dead in an empty home by a process server.
4602784	72	M	3/7/05	2/22/05	15-Day	CS		Benadryl	Intentional Overdose			Child died of combination lethal dose of Benadryl and smothering with a pillow.	Media report of a child been given an intentional overdose.

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[b] HB=Heart Blood; FB= Femoral Blood; LB=Liver Blood; CB=Cavity Blood
[c] PSE=pseudoephedrine; DPH=diphenhydramine; DXM=dextromethorphan; CM=carbinoxamine; BPM=brompheniramine; CPM=chlorpheniramine; APAP=acetaminophen; PPA=phenylpropanolamine
* Date received by manufacturer

Appendix V—Line Listing of AERS Brompheniramine Cases (N=9)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Bromphen-iramine level (mg/L)**	**Cause of Death**	**Description [c]**
437345	1		11/12/86	6/4/86	15-Day	HP	CA	Dimetane DX	cough	2 days		Viral pneumonia	The infant had been born premature and had respiratory problems at birth requiring hospitalization.
4245164	2	F	11/28/03	*2003	15-Day (LIT)	HP			cold		0.4 mg/L (B)	Multiple drug intoxication	The patient was on multiple cough and cold medications. PSE blood level of 14.4 mg/L and DXM blood level of 0.5 mg/L.
332218	3	M	3/26/85	2/28/85	15-Day	HP	NC	Dimetapp	URI	1 dose		SIDS	The infant was given ½ teaspoonfuls for "flu symptoms".
4199574	4		9/25/03	*2003	15-Day (LIT)	HP	NM	Efidac	flu-like symptoms		0.86 mg/L (HB)	Unknown	The caregiver poured medicine from the bottle directly into the infant's mouth. PSE level of 10 mg/L.
524261	6	F	5/16/88	04/??/88	15-Day	HP	MN	Dimetapp	Flu-Like symptoms			Unknown	The infant was reported to have fulminant hepatitis following a flu-like illness for which she was treated with Lincocin, APAP, amoxicillin and Dimetapp. The patient received a liver transplant which resulted in improvement, however, cerebral perfusion scan showed very little cerebral vascular flow.

Appendix V—Line Listing of AERS Brompheniramine Cases (N=9)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Bromphen-iramine level (mg/L)**	**Cause of Death**	**Description [c]**
188187	20	M	6/1/84	2/14/84	Direct	HP		Dimetapp	Otitis media	7 days		Apnea	The infant was on ampicillin and Dimetapp. He was found limp and brought to the ER where he appeared normal and was referred to his physician. The physician saw the patient the next day and placed him on Bactrim and Dimetapp. Patient found gasping for air and died that evening.
1341985	24		6/21/93	*1993	15-Day	HP	MO	Dimetane DX				head trauma sustained in the alleged motor vehicle accident	The case is under criminal investigation. DXM level of 1.2 mg/L (B).
4206049	36	M	10/6/03	*2003	15-Day (LIT)	HP	DC	Pediacare Cough-Cold Liquid	URI	3 days	0.19 mg/L	Unintentional overdose/cardio respiratory arrest	An empty bottle of a cough and cold preparation was found. PSE level of 4.8 mg/L, DXM level of 0.009mg/L, CPM 0.04 mg/L.
4265885	36	M	1/7/04	*2003	15-Day	LYR	CT	Dimetapp				Overdose	The attorney reported that the child had been forcefully administered Dimetapp and unspecified formulation of Triaminic liquid with malicious intent.

[a] CS=Consumer; HP=Health professional (i.e., pharmacist, nurse, MD, etc); LYR=Lawyer
[b] HB=Heart Blood; FB= Femoral Blood; LB=Liver Blood; CB=Cavity Blood
[c] PSE=pseudoephedrine; DPH=diphenhydramine; DXM=dextromethorphan; CM=carbinoxamine; BPM=brompheniramine; CPM=chlorpheniramine; APAP=acetaminophen; PPA=phenylpropanolamine
* Date received by manufacturer

Appendix VI—Line Listing of AERS Chlorpheniramine Cases (N=27)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Chlorpheniramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
3622919	1	M	11/29/00	*2000	Periodic (LIT)	HP	MA	Novahistine DH Liquid/Triaminic syrup	Viral Tracheitis	2 doses		Acute opiate intoxication with contributory findings of severe bronchitis	The patient was born 1 month premature. Postmortem free codeine level: 0.34 mg/L
4382025	1	M	6/17/04	2/19/04	15-Day	CS	TX	Tussionex Pennkinetic	Sleep	1 dose	< 0.25 mg/L (HB)	Acute combined sedative (hydrocodone and chlorpheniramine) toxicity	Media report of a 27 day old premature infant who died after receiving a dose of Tussionex. Hydocodone level of 0.19 mg/L.
682968	2	M	5/14/90	3/12/89	15-Day	LWY	FL	Triaminic Cold Syrup				Shaking of infants' head or prolonged overdoses of Triaminic Cold Syrup	Manner of death was reported as homicide. PPA level was found to be 0.071 mg/L.
4544799	2.5	M	1/4/05	2002	15-Day	LWY	AL	Chlorpheniramine (unspecified formulation)		1 dose	0.07 mg/L	Acute drug intoxication	An autopsy revealed DXM level of 0.38 mg/L. The attorney indicated that the cause of death was acute drug toxicity and the manner of death was homicide.
715085	2	M	5/30/91	11/23/90	15-Day	HP	TX	Triaminic Syrup (chlorpheniramine/ PPA)	Congestion	1 day	0.16 mg/L	Unknown	A pathologist reported an accidental death involving Triaminic Syrup. Per report, autopsy is consistent with SIDS but chlorpheniramine levels were high.

Appendix VI—Line Listing of AERS Chlorpheniramine Cases (N=27)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Chlorpheniramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4205823	4		10/3/03	2002	15-Day	HP (LIT)		Chlorpheniramine (unspecified)			0.07 mg/L	Non-accidental overdose	Pharmacist reported that a 4 month old died due to a malicious act by ingestion of doxepin, CM and CPM.CM of 0.13 mg/L.
621485	6	M	11/9/89	10/8/89	15-Day	HP	IA	Rynatan Pediatric Suspension	Cold symptoms	2 doses		Unknown	The child developed seizures after the 2nd dose of Rynatan (1/2 tsp) that was prescribed in the ER. The patient died nine days after hospitalized. Per hospital staff the AE was not drug related.
792437	7	M	3/5/92	*1992	15-Day	HP	CA	Rynatan-S Pediatric Suspension	Bronchitis	4 days		Unknown/SIDS	The infant had been treated with Triaminic and Diemtapp by the mother prior to Rynatan-S. The reporter stated that "the death was not felt to be drug related".
3822323	9	M	11/8/01	*2001	15-Day	HP (LIT)	MD	Chlorpheniramine			Detected	Mixed drug intoxication	Accidentally, numerous doses of unspecified OTC cough and cold preparations had been given to the infant. PSE level=10 mg/L, PPA level=1.4mg/L, and DXM level=0.6 mg/L.
4236467	10	M	11/14/03	*2003	15-Day	CS		Tylenol (unspecified formulation)			High levels detected	Multiple drug intoxication	High levels of DXM 0.37 mg/L, CPM, DPH, and metocloperamide were detected as well.
4791661	12	M	10/7/05	*2005	15-Day	HP (LIT)	DC	Endagen HD				Unknown	The patient accidentally ingested chlorpheniramine/ hydrocodone up to 20 ml.

Appendix VI—Line Listing of AERS Chlorpheniramine Cases (N=27)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Chlorpheniramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4113558	22	M	5/14/03	6/1/83	Direct	CS	NY	Triaminic (child's)	Stuffy nose	2 doses		Unknown	Patient had been prescribed Triaminic and Lidocaine. The patient was also on Phenobarbital for febrile seizures. Patient was administered 1-2 doses of Triaminic and was found dead the next morning.
4245141	24	M	12/1/03	2002	15-Day	HP		Chlorpheniramine (8mg/5ml)/ Hydrocodone (10mg/5ml)	Therapeutic error	1 dose		Unknown	Patient was prescribed a cough and cold preparation containing hydrocodone and CPM. Patient received a single dose and was found dead 3 hours later. It was found that 10 ml were missing from the bottle.
3917793	24	F	5/17/02	2/20/02	15-Day	CS	CO	Tussionex Pennkinetic				Unknown	The patient with a history of pneumonia received Tussionex that was prescribed for the foster mother. The patient had high levels of hydrocodone in her blood.
4512976	30	F	11/29/04	*2004	15-Day	HP	GA	Tussionex Pennkinetic	Cough				The medication was incorrectly administered by the mother. The autopsy showed toxic narcotic levels. The patient was also prescribed an antibiotic and a decongestant.
4484334	36	F	10/21/04	2003	15-Day	HP (LIT)	DC	Tussionex	Accidental exposure			Accidental overdose	The patient took an unknown amount of oral ibuprofen and Tussionex in an accidental exposure

Appendix VI—Line Listing of AERS Chlorpheniramine Cases (N=27)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Chlorpheniramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
4206049	36	M	10/6/03	*2003	15-Day (LIT)	HP	DC	Pediacare Cough-Cold Liquid	URI	3 days	0.04 mg/L	Unintentional overdose/cardio respiratory arrest	An empty bottle of a cough and cold preparation was found. BPM level 0.19 mg/L, DXM level of 0.009mg/L, and PSE level of 4.8 mg/L
4265885	36	M	1/7/04	*2003	15-Day	LWY	CT	Triaminic Liquid (unknown formulation)				Non-accidental overdose	The patient died from a malicious overdose of an unspecified formulation of Triaminic and Dimetapp.
770110	36	M	7/31/91	*1991	15-Day	HP	WA	Tussionex Pennkinetic				Unknown	The Patient experienced respiratory arrest and subsequently died while taking therapeutic dose of Tussionex. No additional information was provided.
79732	42	F	9/1/75	5/4/75	Periodic	HP	ND	Contac (NDA - 12686)			Detected	Pulmonary edema and cerebral edema secondary to drug ingestion	Per toxicology report, CPM and atropine was detected within the liver.
4086092	48	M	4/2/03	2/1/03	Direct	HP	UT	Tussionex Pennkinetic	URI	2 days	0.4 mg/L	Unknown	The child was found dead after being given 5 ml every 12 hours for 2 days. The prescription was for 2.5ml q12h. Hydrocodone blood level of 0.15 mg/L.

Appendix VI—Line Listing of AERS Chlorpheniramine Cases (N=27)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Chlorpheniramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
5013752	48	M	5/30/06	3/8/06	15-Day	CS		Robitussin Pediatric Night relief				Unknown	According to the patient's mother cause of death was considered overdose. Co-suspect medication included Imodium and Ex-Lax (sennosides) of which the child had consumed an unknown amount.
3975892	48	F	9/11/02	6/2/99	15-Day	CS	NJ	Triaminic Liquid cold & cough	otitis media/post nasal drip	16 days		subarachnoid hemorrage	The patient was on multiple cough and cold medications. Concurrent medications included Ceftin, Cipro, Augmentin, Pediazole, Tylenol and Zithromax.
4224863	48	M	11/3/03	*2003	15-Day (LIT)	HP	DC	Tussend	nasopharyngitis			cardiopulmonary arrest	The patient erroneously received hydrocodone that was prescribed for the father. Hydrocodone level of 0.67 mg/L and CPM level of 0.21 mg/L.
920107	60	F	1/27/94	12/26/88	Periodic	HP	PA	Tussionex ER Supsension	Pneumonia	1 dose		Unknown	A patient with pneumonia received Tussionex and amoxicillin and died later that same night. According to the pharmacist " the drug did not play a role in the child's death"
662950	60	M	5/2/90	5/12/88	Periodic	HP	MA	Tussionex Pennkinetic (unknown if related to 19-111 or 10-768	Cough				A lab technician reported an apparent Tussionex overdose as a result of possible medication error. Hydrocodone level: 0.32 mg/L

Appendix VI—Line Listing of AERS Chlorpheniramine Cases (N=27)													
AERS ISR #	**Age (month)**	**Sex**	**Receive Date**	**Event Date**	**Report Type**	**Source**	**State**	**Trade Name per Report**	**Indication**	**Time to Onset**	**Chlorpheniramine (mg/L)[b]**	**Cause of Death**	**Description [c]**
5084308	72	M	8/17/06	4/11/06	15-Day	HP	SC	Tussionex	Cough	2 doses		Respiratory depression due to drug overdose	The patient died of an accidental overdose. The patient also had a history of asthma.

[a] CS=Consumer; HP=Health professional (i.e., pharmacist, nurse, MD, etc); LYR=Lawyer

[b] HB=Heart Blood; FB= Femoral Blood; LB=Liver Blood; CB=Cavity Blood

[c] PSE=pseudoephedrine; DPH=diphenhydramine; DXM=dextromethorphan; CM=carbinoxamine; BPM=brompheniramine; CPM=chlorpheniramine; APAP=acetaminophen; PPA=phenylpropanolamine

* Date received by manufacturer

Appendix VII- Ingredients for Cough and Cold Medications Presented in this Consult *						
Drug Name	**Rx/OTC**	**Approved/ Unapproved**	**Decongestant**	**Antihistamine**	**Cough Suppressant**	**Other Medication**
Vicks 44E Cough/Chest Congestion Relief Syrup/ 15 ml	OTC				Dextromethorphan 20mg	Guaifenesin 200mg, ethanol 5%
Actifed Syrup/5 ml	OTC	Approved	Pseudoephedrine 30mg	Triprolidine 1.25 mg		
Actifed-C/ 5ml	Rx	Approved	Pseudoephedrine 30 mg	Triprolidine 1.25 mg		codeine 10mg
Benadryl Allergy/Sinus	OTC		Unspecified formulation			
Carbaxefed DM/RF/ 1 ml	Rx	Unapproved	Pseudoephedrine 15 mg	Carbinoxamine 1 mg		
Cardec DM Drops/ 1 ml	Rx	Unapproved	Pseudoephedrine 25 mg	Carbinoxamine 2 mg	Dextromethorphan 4mg	
Cardec DM Syrup/5 ml	Rx	Unapproved	Pseudoephedrine 60mg	Carbinoxamine 4mg	Dextromethorphan 15 mg	
Infant Tylenol Cold Plus Drops/ 1.6 ml	OTC		Pseudoephedrine 15 mg		Dextromethorphan 5 mg	Acetaminophen 160 mg
Dimetane DX	Rx	Approved	Pseudoephedrine 30mg	Brompheniramine 2mg	Dextromethorphan 10mg	
Dimetapp Elixir	OTC	Approved	Phenylpropanolamine 12.5 mg	Brompheniramine 2 mg		
Efidac	Rx	Approved	Pseudoephedrine 240 mg			
Infant's Pediacare Decongestant and Cough	OTC		Unable to identify ingredients			
Novahistine DH Liquid/5 ml	Rx	Unapproved	Pseudoephedrine 30mg	Chlorpheniramine 2 mg		Codeine 10mg, 5% alcohol
Pediacare cough/cold liquid	OTC		Unspecified formulation			

Appendix VII- Ingredients for Cough and Cold Medications Presented in this Consult *						
Drug Name	**Rx/OTC**	**Approved/ Unapproved**	**Decongestant**	**Antihistamine**	**Cough Suppressant**	**Other Medication**
Phenergan VC with Codeine /5ml	Rx	Approved	Phenylephrine 5 mg	Promethazine 6.25 mg		Codeine 10 mg
Robitussin PM Cough & Cold/5 ml	OTC		Pseudoephedrine 15 mg	Chlorpheniramine 1 mg	Dextromethorphan 7.5 mg	
Robitussin Pediatric cough and cold/ 5ml	OTC		Pseudoephedrine 15 mg		Dextromethorphan 7.5 mg	
Rondec oral drops/ 1 ml	Rx	Unapproved	Pseudoephedrine 25 mg	Carbinoxamine 2mg		
Rondec DM oral drops/1 ml	Rx	Unapproved	Pseudoephedrine 25 mg	Carbinoxamine 2 mg	Dextromethorphan 4 mg	
Rondec Syrup/5 ml	Rx	Unapproved	Pseudoephedrine 60 mg	Carbinoxamine 4 mg		
Sudafed	OTC		Pseudoephedrine 30 mg			
Triaminic Liquid cold & cough/ 5 ml	OTC		Pseudoephedrine 15 mg	Chlorpheniramine 1 mg	Dextromethorphan 7.5mg	
Tussend/ 5 ml	Rx	Unapproved	Pseudoephedrine 30 mg	Chlorpheniramine 2.5 mg		Hydrocodone 2 mg
Tussionex Pennkinetic/5ml	Rx	Approved		Chlorpheniramine 8 mg		Hydrocodone 10 mg

* Some of these products have been reformulated over the years but have maintained the same trade name

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 17, 2007
To:	Andrea Leonard-Segal, M.D., M.S., Director Division of Nonprescription Clinical Evaluation, HFD-560
Thru:	Ann McMahon, M.D., M.S., Deputy Director For Mark Avigan, M.D., C.M., Director Division of Drug Risk Evaluation, HFD-430
From:	Gita Akhavan-Toyserkani, Pharm.D., MBA, Safety Evaluator Yoo Jung Chang, Pharm.D., Safety Evaluator Syed Rizwanuddin Ahmad, M.D., M.P.H, F.I.S.P.E, Medical Epidemiologist Division of Drug Risk Evaluation, HFD-430
Subject:	Postmarketing safety review of serious adverse events in children less than 6 years of age associated with the use of cough and cold medications
Drug Name(s):	pseudoephedrine, chlorpheniramine, diphenhydramine, and dextromethorphan
OSE RCM #:	2007-1022

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CONTENTS

EXECUTIVE SUMMARY

This consult is in response to a request from the Division of Nonprescription Clinical Evaluation (DNCE) to review the Adverse Event Reporting System (AERS) database for U.S. reports of serious adverse events in children under 6 years of age associated with the use of pseudoephedrine, chlorpheniramine, diphenhydramine, and dextromethorphan. In addition, data from the Toxic Exposure Surveillance System (TESS), a poisoning surveillance database maintained and owned by the American Association of Poison Control Centers (AAPCC), were reviewed to determine the extent of poisoning in association with exposure to cough and cold products.

On March 1, 2007, the Baltimore City Health Department submitted a citizen's petition stating that the over-the-counter (OTC) cough and cold medications are neither safe nor effective for use in young children and requested that the FDA take action by amending 21 CFR 341, the Final Monograph for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products, to state that the OTC cough and cold medications have not been found to be safe nor effective in children under six years of age and therefore should not be used in this population. Currently, the dosing information is provided on the labeling of decongestants, antitussives, and expectorants for children 2 years of age and older; antihistamines are labeled with directions for use in children 6 years and older. For younger children, the parent is directed to consult a physician. An advisory committee meeting is scheduled for October 18 - 19, 2007 to discuss the safety and efficacy of cough and cold medications in the pediatric population and to discuss what, if any, action needs to be taken at this time.

The AERS database was searched for domestic reports of serious adverse events specifically related to the nervous, cardiac, and respiratory systems involving children under 6 years of age associated with pseudoephedrine, chlorpheniramine, diphenhydramine, and dextromethorphan; these 4 drugs were selected because they retrieved the highest numbers of AERS reports among the pediatric cough and cold products. Only the last 5 years were searched in the AERS database (01/01/2002 – 05/11/2007). This time frame was selected to focus on the most relevant cases, as many OTC cough and cold products have been reformulated throughout the years. The highlights of the AERS review are summarized below:

- The number of unique domestic cases of serious adverse events associated with each drug is as follows: pseudoephedrine 150, chlorpheniramine 63, diphenhydramine 83, and dextromethorphan 105.
- Approximately 30% of the serious adverse event cases associated with pseudoephedrine, chlorpheniramine, diphenhydramine, or dextromethorphan reported a death outcome.
- Over 50% of the reported serious adverse events associated with pseudoephedrine and dextromethorphan occurred in children less than 2 years of age.
- Over 50% of the reported serious adverse events associated with chlorpheniramine and diphenhydramine occurred in children 2 to 5 years of age.
- Both OTC and prescription products were reported cases; however, the majority of the cases were associated with the use of an OTC cough and cold product (56-78%). The use of a prescription cough and cold product was reported in 14% of the cases.
- More than 75% of the reports associated with pseudoephedrine, chlorpheniramine, and dextromethorphan involved the use of a multi-ingredient cough and cold product.

- Drug overdoses associated with pseudoephedrine, chlorpheniramine, diphenhydramine, or dextromethorphan contributed to serious adverse events in approximately 48% of the cases.
    - Approximately 22% of the cases reported an **accidental exposure** that resulted in a serious adverse event.
    - Approximately 6% of the cases reported an **intentional overdose** by a caregiver resulted in a serious adverse event.
    - Approximately 16% of the cases reported a **medication error** that resulted in a serious adverse event to include prescribing errors, dispensing errors, administration errors, duplication of therapy, and wrong drug administration.
    - The manner of overdose could not be determined in the remaining 56% of the cases.
- Serious adverse events and deaths related to the nervous system, cardiac system, respiratory system, and other notable events have been reported with overdoses of cough and cold medications as well as in cases where the dose did not exceed the labeled dose for the lowest age group.
    - In particular, convulsions have been reported with the administration of cough and cold medications, more commonly in children 2 years of age and older. Convulsions were more common in settings outside of an overdose.
    - Serious cardiac events (cardiac arrest, cardio-respiratory arrest, cardiac failure, tachycardia, supraventricular tachycardia) and respiratory events (respiratory distress, respiratory arrest, respiratory failure, dyspnea, apnea) have been reported following the ingestion of cough and cold medications mostly in the setting of a drug overdose. However, serious cardiac and respiratory events were reported in cases where the dosage did not exceed the labeled dose for the lowest age group.

There are limitations of quantitatively analyzing a spontaneous reporting database such as AERS. One limitation is that an adverse event report may contain concomitant use of other medications and/or multiple ingredient products, and therefore, a clear drug-event association is often difficult to establish. The decongestant, antihistamine, and antitussive discussed in this consult are found in many OTC preparations either as single-ingredient preparations, or more commonly in combination of at least two or more ingredients. Other limitations include underreporting and the length of time the product has been on the market. Under 21 CFR 341 there were no reporting requirements for OTC monograph products for the time period searched in AERS, which makes it especially difficult to obtain a true number of adverse events (numerator) for these products. There are legislative changes that will be effective December 22, 2007 that will require manufacturers of dietary supplements and over-the-counter monograph products to submit serious adverse event reports to the FDA.

An analysis of overdose and poisoning-related therapeutic misadventures in association with 'cough and cold' and diphenhydramine preparations as recorded in the TESS database accounted for about 110,000 calls in 2001 and increased to 147,000 calls in 2005. Approximately 40-60% of these calls involve children < 6 years of age. In the last 5 years, there were a total of 14 deaths attributed to 'cough and cold' and diphenhydramine preparations in children < 6 years of age recorded to the TESS database. The majority of these cases were associated with unintentional poisoning. Both OTC and prescription products have been involved in these poisoning/overdose cases. Notably, 4 of the 14 deaths were associated with the ingestion of a combination product

containing chlorpheniramine and hydrocodone. Because of the problem of underreporting of poisoning/overdose cases, the true number of cases may be considerably higher.

In conclusion, both the AERS and TESS postmarketing data suggest that the use of prescription and OTC cough and cold medication in children younger than 6 years of age have been associated with serious adverse events, including death. Therefore, we recommend an educational campaign directed towards healthcare providers and parents/caregivers that addresses proper education about cough and cold products; in particular, the risks of using these products in children less than the minimum age recommended in the monograph, as well as the potential risk of overdose when using multiple cough and cold products. With the known lack of evidence of efficacy in children and in view of the current safety data on the potential for drug toxicity, the labeling of cough and cold products (both prescription and OTC) should include prominent language to describe the risk of overdose in children. Also, the statement "consult a physician" for decongestants and antitussives in patients under 2 years of age and in patients under 6 years of age for antihistamines should be reconsidered. In the absence of specific dosing instructions, we suggest that the revised wording state that dosing is not recommended in these age groups. Further, a timely forum among stakeholders is recommended to discuss making only single ingredient cough and cold products available for pediatric formulations.

1 BACKGROUND

1.1 INTRODUCTION

This consult is in response to a request from the Division of Nonprescription Clinical Evaluation (DNCE) to review the Adverse Event Reporting System (AERS) database for reports of serious adverse events in children less than 6 years of age associated with the use of pseudoephedrine, chlorpheniramine, diphenhydramine, and dextromethorphan. On March 1, 2007, the Baltimore City Health Department submitted a citizen's petition stating that the over-the-counter (OTC) cough and cold medications are neither safe nor effective for use in young children and requested that the FDA take action by amending 21 CFR 341, the Final Monograph for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products, to state that the OTC cough and cold medications have not been found to be safe nor effective in children under the age of six years, and therefore, should not be used in this population. Currently, the dosing information is provided on the labeling of decongestants, antitussives, and expectorants for ages 2 years and older. Antihistamines are labeled with dosing information for children 6 years and older. For younger children, the parent is directed to consult a physician. An advisory committee meeting is scheduled for October 18th and 19th 2007 to discuss the safety and efficacy of cough and cold medications in children. In addition to the current safety review, the Division of Drug Risk Evaluation (DDRE) recently completed a review of the AERS database for reports of pediatric fatalities (≤ 6 years of age) associated with the use of pseudoephedrine, phenylephrine, ephedrine, diphenhydramine, brompheniramine, and chlorpheniramine; this review recommended that these products should not be given to young children (under 2 years for decongestants and under 6 years for antihistamines) due to the lack of evidence of efficacy and safety of the products. The AERS postmarketing data suggest that the use of OTC and prescription cough and cold medications in young children, particularly in children less than 2 years of age, could result in fatal overdoses.[1]

The OTC and prescription cough and cold medicines containing decongestants, antihistamines, and antitussives are prescribed widely by general pediatricians to offer relief from the symptoms of the common cold.[2] More than 800 cough/cold preparations, including pediatric preparations, are available in the United States.[3] Cough and cold preparations are among the most common substances administered to the pediatric population and reported to the poison control centers; data from the 2005 annual report of the American Association of Poison Control Centers indicate that of the 1,233,695 poison exposures in children younger than 6 years of age, 70,398 (5.7%) were exposures to cough and cold preparations (accidental and non-accidental).[4]

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[1] Akhavan-Toyserkani G. Safety Review: Infant mortality associated with the use of cough and cold medications. DDRE/OSE/FDA. February 6, 2007.

[2] Carr BC. Efficacy, abuse, and toxicity of over-the-counter cough and cold medicines in the pediatric population. Curr Opin Pediatr . 2006;18:184-188.

[3] Kelly LF. Pediatric cough and cold preparations. Pediatrics in Review. 2004;25(4):115-23.

[4] Lai MW, Klein-Schwartz W, Rodgers GC, Abrams JY, Haber DA, Bronstein AC, Wruk KM. 2005 annual report of the american association of poison control centers' national poisoning and exposure database. Clinical Toxicology, 2006;44:803-932.

Several articles regarding the safety and efficacy of the over-the-counter cough and cold medicines in children have been published.[5,6,7] In January of 2007, the Center for Disease Control and Prevention (CDC) in collaboration with the FDA issued a Morbidity and Mortality Weekly Report (MMWR) article describing three deaths in U.S. infants associated with unintentional overdoses of cough and cold medications.[8] In March 2007, the Journal of Forensic Sciences published an article describing the deaths of 15 children ages sixteen months or younger where a drug commonly found in OTC cold preparations was determined to be either the cause of death or a contributing factor in the majority of the cases.[9] In addition to recent articles detailing safety concerns of cough and cold medicine use in children, the Agency has taken steps to ensure the safety of children by revising the labeling of carbinoxamine use in pediatric patients. In March 2006, the Division of Pulmonary and Allergy Drug Products (DPADP) completed a Health Hazard Evaluation (HHE) regarding the use of prescription cough and cold products containing carbinoxamine maleate and pseudoephedrine hydrochloride (PSE) with or without dextromethorphan (in patients less than 1 year of age). The revised labeling recommends carbinoxamine use only in 2 years and above.[10]

In this consult, DNCE requested that we review cases with serious adverse events in children less than 6 years of age, and focus specifically on neurologic, cardiac, and respiratory adverse events.

1.2 REGULATORY HISTORY

The passage of the Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act established that all marketed drugs provide proof of effectiveness and safety, including OTC medications that were already on the market. The approval process for the cough and cold products began in 1976 with input from an expert advisory panel. The external advisory panel recognized that there was limited data on most cough and cold drugs in the monograph titled "Cold, Cough, Allergy, Bronchodilator and Anti-Asthmatic Drug Products for Over-the-Counter Human Use" (CCABA). They also recognized the difficulties of conducting clinical trials to determine the appropriate drug doses in children. Despite the lack of data, standard pediatric dosage recommendations were necessary because OTC cough and cold medications were widely used in children, and updates would be made with the availability of new data. To accomplish this, the expert advisory panel sought the assistance of a "Special Panel on Pediatric Dosage," comprised of seven physicians. The Special Panel review and expert advisory panel provided the following recommendations for the CCABA:

- For infants under 2 years of age, the pediatric dosage should be established by a physician;

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[5] Marinetti L, Lehman L, Casto B, Harshbarger K, Kubiczek P, Davis J. Over-the-counter cold medications - postmortem findings in infants and the relationship to cause of death. Journal of Analytical Toxicology. 2005;29(7):738-43.

[6] Bhatt-Mehta V. Over-the-counter cough and cold medicines: Should parents be using them for their children? Annals of Pharmacotherapy. 2004;38(11):1964-6.

[7] Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of over-the-counter cough and cold medications. Pediatrics. 2001;108(3).

[8] Centers for Disease Control and Prevention. 2007. Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005. *M.M.W.R.* 56 (01);1-4.

[9] Wingert WE, Mundy LA, Collins GL, Chmara ES. Possible Role of Pseudoephedrine and Other Over-the-Counter Cold Medications in the Deaths of Very Young Children

[10] DPADP Review: Starke P. Health Hazard Evaluation Consult for cough/cold products containing carbinoxamine maleate and pseudoephedrine hydrochloride. March 3, 2006.

- For children 2 to under 6 years of age, the pediatric dosage is 1/4 the adult dosage;

- For children 6 to under 12 years of age, the dosage is 1/2 the adult dosage.

The Panel recommended that the dosing for CCABA antihistamines should not be labeled for use in children under the age of 6, except as part of the professional labeling (labeling intended for healthcare professionals but not to the public). The FDA, with input from an external advisory panel of experts, developed the dosing and labeling recommendations for these products that were published in the monograph titled "Cold, Cough, Allergy, Bronchodilator and Anti-Asthmatic Drug Products for Over-the-Counter Human Use." These regulations can be found in 21 CFR 341 (http://www.access.gpo.gov/nara/cfr/ waisidx_06/21cfr341_06.html).

In past years, because there were no adverse event reporting requirements for OTC monograph cough and cold products, as required for prescription products, the number of adverse events for these OTC products may have been grossly underreported. However, recent legislative changes, effective December 22, 2007, will require manufacturers of dietary supplements and over-the-counter products to submit serious adverse event reports to the FDA.[11] There have been other recent legislative changes that have affected the OTC cough and cold products. Pseudoephedrine is a decongestant commonly found in cough and cold preparations, but its notoriety as a methamphetamine precursor has led some state governments to restrict its sale. The Combat Methamphetamine Epidemic Act (CMEA) of 2005 was signed into Law on March 9, 2006 to regulate, among other things, retail over-the-counter sales of ephedrine and pseudoephedrine products.[12] Retail provisions of the CMEA include placement of the product out of direct consumer access, daily sales limits, monthly purchase limits, and maintenance of sales log books. There have also been recent efforts on the part of the Agency to remove unapproved products that contain carbinoxamine. Many prescription cough and cold products containing carbinoxamine are marketed without approved applications and are inappropriately labeled for use in infants and young children. A Health Hazard Evaluation regarding the use of cough and cold products containing carbinoxamine maleate and pseudoephedrine hydrochloride was posted in March 2006 and resulted in a Federal Registry notice announcing the removal of all unapproved drug products containing carbinoxamine from the market.

1.3 PRODUCT LABELING

1.3.1 Decongestant

Decongestants cause vasoconstriction of blood vessels in the nasal mucosa. These medications target α as well as β receptors, which explains their potential side effects, including tachycardia and hypertension.[13] Alpha-adrenergic agonists are used extensively as nasal decongestants in allergic rhinitis and in acute rhinitis in patients with upper respiratory infections.[14]

Pseudoephedrine (PSE) hydrochloride is a stereoisomer of ephedrine that is less potent than ephedrine in producing tachycardia, increased blood pressure, and CNS stimulation. PSE is an α-

[11] The Dietary Supplement and Nonprescription Drug Consumer Protection Act was signed into law on December 22, 2006

[12] http://www.deadiversion.usdoj.gov. Accessed September 26, 2006.

[13] Phenylpropanolamine (PPA) is a decongestant that was taken off the market in November 2006 because of its association with cardiomyopathy and intracranial hemorrhage.

[14] Goodman & Gilman's The Pharmacological Basis of Therapeutics - 11th Ed. (2006). Accessed online 9/18/2006.

and, to a lesser extent, β-adrenergic receptor agonist. Because of the predominant α–adrenergic properties on the arterioles that supply the nasal mucosa, it is used primarily as a nasal decongestant. Pseudoephedrine is found in many OTC preparations either as single-ingredient preparations, or more commonly in combination with antihistamines, acetaminophen and/or ibuprofen.

Labeling for oral nasal decongestants as stated in the OTC monograph for children 2 to 12 years of age include:

- Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor.
- If symptoms do not improve within 7 days or are accompanied by fever, 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.
- **Pseudoephedrine** (oral nasal decongestant) - Children 6 years to under 12 years of age: 30 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 2 to under 6 years of age: 15 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children under 2 years of age: consult a doctor.

1.3.2 Antihistamines

The first-generation antihistamines block H1 receptors on nasal vasculature and compete with histamine for receptor sites. They can also cross the blood-brain barrier and affect the central nervous system (CNS).[15] **Diphenhydramine** and **chlorpheniramine** are H1 antagonists available in numerous over-the-counter preparations. The drying action of the mucous membranes is due to the anticholinergic properties of the first-generation antihistamines. Diphenhydramine often used for its sedative effects in adults, can cause paradoxical central nervous system stimulation in children, with effects ranging from excitation to seizures and death.

Labeling for antihistamines as stated in the OTC monograph for children 6 to 12 years of age include:

- 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.
- **Chlorpheniramine** - 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.
- **Diphenhydramine**
    - 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 use with any other product containing diphenhydramine, even one used on skin.
- **Chlorpheniramine** maleate (oral) - Children 6 years to under 12 years of age: oral dosage is 2 mg every 4 to 6 hours, not to exceed 12 mg in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.
- **Diphenhydramine** hydrochloride (oral) - Children 6 years to under 12 years of age: oral dosage is 12.5 to 25 mg every 4 to 6 hours, not to exceed 150 mg in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

[15] Kelly LF. Pediatric cough and cold preparations. Pediatrics in Review. 2004;25(4):115-23.

1.3.3 Antitussives

Dextromethorphan is an opioid derivative with antitussive activity and little to no analgesic, addictive, or CNS depressive properties.[16] It acts by elevating the threshold for cough in the medulla oblongata. Dextromethorphan is a common ingredient in OTC cough and cold products and is used for the temporary relief of cough caused by minor throat and bronchial irritation. Adverse events with dextromethorphan are rare, but there have been reports of significant morbidity and mortality, especially in young children.[17]

Diphenhydramine, previously described in the antihistamine section, is also used as an antitussive.

Labeling for antitussives as stated in the OTC monograph for children 2 to 12 years of age include:

- Do not give this product for persistent or chronic cough such as occurs with asthma or if cough is accompanied by excessive phlegm unless directed by a doctor.
- If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor.
- **Dextromethorphan** hydrobromide (oral) - Children 6 years to under 12 years of age: 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours, not to exceed 600 mg in 24 hours. Children 2 years to under 6 years of age: 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. Children under 2 years of age: consult a doctor.
- **Diphenhydramine**
    - 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.
    - 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 use with any other product containing diphenhydramine, even one used on skin.
    - **Diphenhydramine** hydrochloride (oral) - Children 6 years to under 12 years of age: oral dosage is 12.5 mg every 4 hours, not to exceed 75 mg in 24 hours, or as directed by a doctor. Children under 6 years of age: consult a doctor.

2 AERS CRUDE COUNTS

2.1 SEARCH CRITERIA FOR AERS CRUDE COUNTS

The AERS database was searched for U.S. reports of all adverse events and serious adverse events, including deaths associated with medications commonly found in pediatric cough and cold products (pseudoephedrine, phenylephrine, ephedrine, diphenhydramine, chlorpheniramine, brompheniramine, guaifenesin, and dextromethorphan) from the beginning of AERS collection (1969) to July 11, 2007. The combination products field was selected to include reports associated with the use of single ingredient and combination products. The following age groups were selected:

- children less than 6 years of age

[16] American Hospital Formulary Service Drug Information, 1999. American Society of Health-System Pharmacists.

[17] Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl);260S-283S.

- children 6 – 17 years of age
- adults 18 years of age and up

2.2 RESULTS FOR AERS CRUDE COUNTS

Crude counts may include duplicates and the reported adverse events may not be directly related to the suspected cough and cold product. In this section, individual reviews were not performed to determine an association between the reported events and the use of cough and cold medications, primarily due to the large number of the reported adverse event cases.

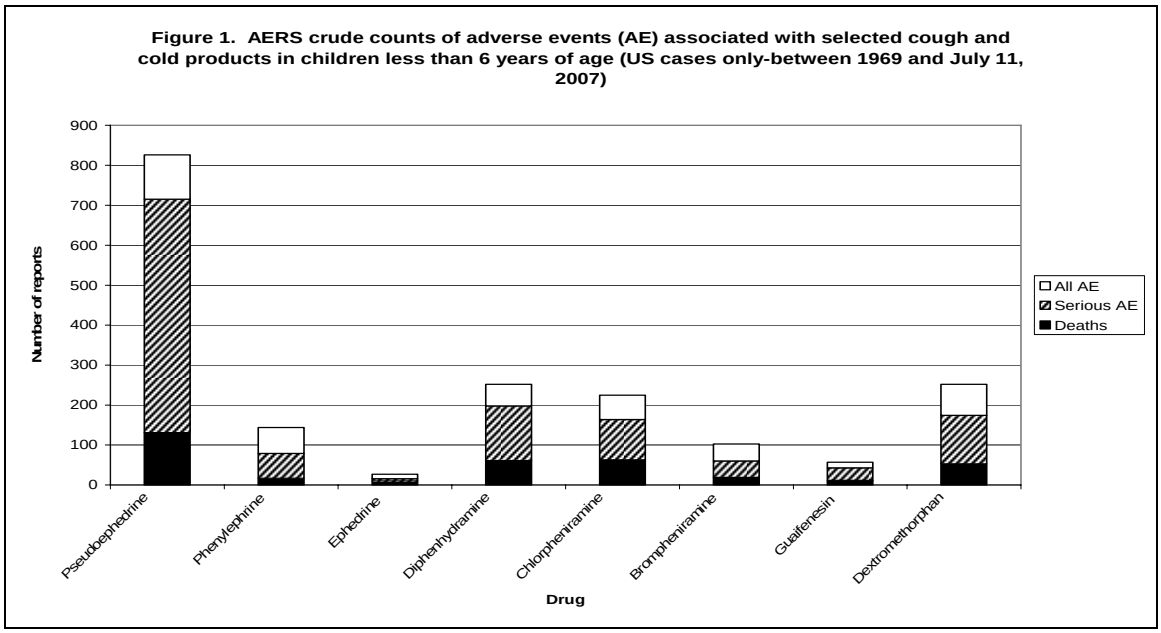
Table 1. Crude Counts[1] of AERS Reports Associated with Active Ingredients found in Pediatric Cough and Cold Products, Stratified by Age Groups (U.S. cases only - between 1969 and July 11, 2007)

Drug	Age	All reports	Serious[2]	Death
Pseudoephedrine	> 18 yrs	7091	5036 (71%)	543 (8%)
	6 – 17 yrs	583	402 (69%)	45 (8%)
	< 6 yrs	826	715 (87%)	131 (16%)
Phenylephrine	> 18 yrs	1886	1452 (77%)	87 (5%)
	6 – 17 yrs	164	106 (65%)	18 (11%)
	< 6 yrs	144	79 (55%)	17 (12%)
Ephedrine	> 18 yrs	385	252 (65%)	127 (33%)
	6 – 17 yrs	31	8 (26%)	2 (6%)
	< 6 yrs	27	16 (59%)	10 (37%)
Diphenhydramine	> 18 yrs	2868	2416 (84%)	1051 (37%)
	6 – 17 yrs	307	237 (77%)	79 (26%)
	< 6 yrs	252	198 (78%)	61 (24%)
Chlorpheniramine	> 18 yrs	3324	2353 (71%)	225 (6.8%)
	6 – 17 yrs	340	256 (75%)	32 (9.4%)
	< 6 yrs	225	164 (73%)	63 (28%)
Brompheniramine	> 18 yrs	1340	1075 (80%)	70 (5.2%)
	6 – 17 yrs	95	64 (67%)	16 (17%)
	< 6 yrs	103	60 (58%)	19 (18%)
Guaifenesin	> 18 yrs	1378	1152 (84%)	109 (7.9%)
	6 – 17 yrs	117	81 (69%)	19 (16%)
	< 6 yrs	57	43 (75%)	12 (21%)
Dextromethorphan	> 18 yrs	1387	1165 (84%)	203 (15%)
	6 – 17 yrs	159	121 (76%)	27 (17%)
	< 6 yrs	252	174 (69%)	53 (21%)

[1] May include duplicates.

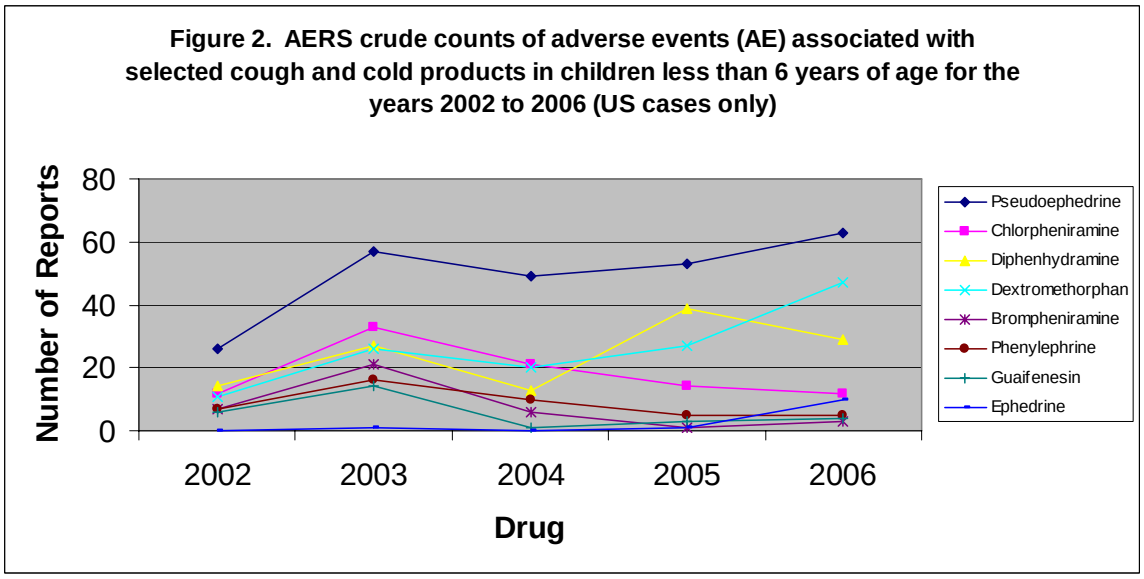
[2] Adverse events with a serious outcomes per regulatory definition, includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

Figure 1 summarizes the data from Table 1 for patients < 6 years of age.



The highest numbers of crude reports were associated with pseudoephedrine, diphenhydramine, dextromethorphan, and chlorpheniramine. A detailed review of these medications is in section 3 (the AERS analysis section) of this document.

Figure 2 below shows the number of crude reports received by the Agency in the past five calendar years (2002 – 2006).



Pseudoephedrine had the highest crude count numbers of all adverse event reports from 2002 to 2006, compared to the other cough and cold medications. Chlorpheniramine, diphenhydramine and dextromethorphan, in addition to pseudoephedrine, rounded out the top four medications with the highest number of crude reports. The crude numbers of reports for pseudoephedrine, dextromethorphan, diphenhydramine, and ephedrine have trended upward from 2002 to 2006; while chlorpheniramine, brompheniramine, phenylephrine, and guaifenesin reports have trended down.

The most commonly reported adverse events {preferred terms (PT)} were generated from all adverse event crude counts for the above selected cough and cold medications. Tables 2 and 3 below lists the top ten PTs for each cough and cold medication.

Table 2. Top 10 PTs from AERS crude counts associated with cough and cold medications in children less than 6 years of age (US cases only - between 1969 and July 11, 2007)

Pseudoephedrine	Phenylephrine	Ephedrine	Diphenhydramine
Accidental Overdose (98)	Convulsion (10)	Drug Toxicity (7)	Coma (19)
Vomiting (91)	Cerebrovascular Accident (8)	Cardiac Arrest (4)	Accidental Overdose (18)
Dermatitis (43)	Apnoea (7)	Loss of Consciousness (4)	Medication Error (18)
Urticaria (43)	Vomiting (6)	Drug Screen Positive (2)	Accidental Exposure (16)
Drug Toxicity (36)	Bradycardia (5)	Laryngospasm (2)	Vomiting (16)
Drug Ineffective (35)	Cyanosis (5)	Pulmonary Congestion (2)	Convulsion (15)
Medication Error (34)	Cough (4)	Accidental Drug Intake By Child (1)	Drug Toxicity (15)
Overdose (34)	Encephalomalacia (4)	Accidental Overdose (1)	Hallucination (15)
Convulsion (33)	Injury (4)	Acute Hepatic Failure (1)	Overdose (14)
Face Oedema (24)	Insomnia (4)	Apnoea (1)	Somnolence (14)

Table 3. Top 10 PTs from AERS crude counts associated with cough and cold medications in children less than 6 years of age (US cases only - between 1969 and July 11, 2007)

Chlorpheniramine	Brompheniramine	Guaifenesin	Dextromethorphan
Convulsion (29)	Convulsion (11)	Convulsion (6)	Convulsion (25)
Coma (15)	Cerebrovascular Accident (8)	Cerebrovascular Accident (5)	Drug Toxicity (21)
Medication Error (15)	Apnoea (5)	Coma (5)	Medication Error (12)
Vomiting (15)	Coma (5)	Maternal Drug Affecting Foetus (5)	Overdose (12)
Accidental Overdose (14)	Medication Error (5)	Medication Error (4)	Accidental Drug Intake By Child (11)
Lethargy (12)	Drug Toxicity (4)	Cleft Lip (3)	Vomiting (11)
Cardio-respiratory Arrest (9)	Encephalomalacia (4)	Cleft Palate (3)	Accidental Overdose (10)
Cyanosis (9)	Injury (4)	Injury (3)	Lethargy (10)
Drug Toxicity (9)	Insomnia (4)	Subarachnoid Haemorrhage (3)	Somnolence (8)
Death (8)	Overdose (4)	Vomiting (3)	Death (7)

Convulsion was reported as the most frequent adverse event in 5 of 8 cough and cold medications (phenylephrine, chlorpheniramine, brompheniramine, guaifenesin, and dextromethorphan); two other cough and cold medications (pseudoephedrine and diphenhydramine) reported convulsion as one of the top 10 reported adverse events. Accidental overdose was reported as the most frequent adverse event for pseudoephedrine; four other cough and cold medications (ephedrine, diphenhydramine, chlorpheniramine, and dextromethorphan) reported accidental overdose as one of the 10 most frequently reported adverse events. Other commonly reported adverse events included drug toxicity, medication error, and overdose.

3 AERS INDIVIDUAL CASE REVIEW

3.1 SELECTION OF CASE SERIES

On May 11, 2007, the AERS database was searched using the ingredient names, pseudoephedrine, chlorpheniramine, diphenhydramine, and dextromethorphan, for all serious adverse event cases that were reported to the Agency in the past five years (01/01/2002 – 05/11/2007) involving children under 6 years of age. This time frame was selected to focus on the most relevant cases, as many OTC cough and cold product have been reformulated throughout the years. The cases were limited to U.S. cases and the concomitant field was selected to include reports associated with the use of single ingredient as well as combination products. The cases were individually reviewed and duplicates were consolidated. The table below presents the number of cases retrieved from the AERS database for each ingredient and the number of cases that were included in the final review after exclusions:

Table 4. Selection of Individual AERS Cases

Drug Name	Crude Counts	Cases Excluded (*n*)	Number of Cases Included
Pseudoephedrine	263	• Duplicates (*46*) • Report associated with litigation of Phenylpropanolamine containing products (*1*) • Reports associated with unspecified Tylenol product without evidence of pseudoephedrine involvement (*42*) • Reports without evidence of pseudoephedrine as a contributory product (*6*) • Reports associated with in utero exposure (*12*) • Report associated with expired medication (*1*) • Reports without an adverse event (*5*)	150
Chlorpheniramine	90	• Duplicates (*12*) • Report associated with litigation of Phenylpropanolamine containing products (*4*) • Reported age is greater than 5 years (*1*) • Reported product does not contain chlorpheniramine (*9*) • Report without evidence of chlorpheniramine as a contributory product (*1*)	63
Diphenhydramine	128	• Duplicates (*22*) • Report associated with in utero exposure (*6*) • Report associated with intravenous or topical route of administration (*7*) • Reported age is greater than 5 years (*2*) • Report uncertain of diphenhydramine exposure (*1*) • Report without evidence of diphenhydramine as a contributory product (*5*) • Report confounded by motor vehicle accident (*1*) • Report associated with strangulation (*1*)	83
Dextromethorphan	128	• Duplicates (*15*) • Reported product does not contain dextromethorphan (*2*) • Report without evidence of dextromethorphan as a contributory product (*6*)	105

3.2 RESULTS FOR INDIVIDUAL CASE REVIEW

3.2.1 Pseudoephedrine

An AERS search for reports of pediatric serious adverse events associated with pseudoephedrine from the past five years (1/1/2002 – 5/11/2007) retrieved 150 unique domestic spontaneous cases. The reported adverse events in the cases were categorized according to the AERS system organ class (SOC) as listed below *(a report may contain more than one adverse event term)*:

System Organ Class	Preferred Terms (*n*)
Cardiac disorders (17)	cardiac arrest (3), cardiac disorder (3), cardiac failure (1), cardio-respiratory arrest (4), cyanosis (1), myocarditis (1), supraventricular tachycardia (2), tachycardia (2)
Ear and labyrinth disorders (1)	ear pain (1)
Endocrine disorders (1)	diabetes mellitus (1)
Eye disorders (11)	blepharospasm (1), eye pain (1), eye disorder (2), erythema of eyelid (1), mydriasis (4), strabismus (1), vision blurred (1)
Gastrointestinal disorders (19)	abdominal pain (1), diarrhea (1), constipation (2), food intolerance (1), gingival swelling (1), nausea (2), vomiting (11)
General disorders and administration site conditions (32)	cold sweat (1), condition aggravated (4), death (2), drug interaction (1), edema (1), fatigue (1), gait disturbance (1), hyperhidrosis (3), listless (4), malaise (1), pharmaceutical product complaint (4), pyrexia (2), sudden infant death syndrome (5), swelling (1), therapeutic response unexpected (1), unevaluable event (1)
Hepatobiliary disorders (3)	hepatic steatosis (1), jaundice (1), liver disorder (1)
Immune system disorders (12)	hypersensitivity (5), anaphylactic shock (2), Steven-Johnson Syndrome (1), face edema (1), drug hypersensitivity (1), radioallergosorbent test positive (1), generalized edema (1)
Infections and infestations (9)	bronchitis (1), croup infectious (1), influenza (1), meningitis (1), nasopharyngitis (1), pneumonia (3), pharyngitis (1)
Injury, poisoning and procedural complications (80)	accidental exposure (11), accidental drug intake by child (21), drug toxicity (17), drug dispensing error (1), fall (2), head injury (1), incorrect dose administration (1), medication error (9), multiple drug overdose (3), overdose (12), poor quality drug administered (1), wrong dose administered (1)
Investigations (39)	bacteria urine identified (1), blood pH decreased (1), blood glucose decreased (1), blood glucose increased (1), blood potassium increased (1), blood sodium increased (1), drug level above therapeutic (1), drug screen false positive (1), toxicologic test abnormal (2), laboratory test interference (1), urine amphetamine (1), heart rate increased (8), blood pressure increased (2), respiratory rate increased (5), white blood cell count positive (2), drug screen positive (3), drug level increased (1), electrocardiogram abnormal (1), false positive laboratory test (2), body temperature increased (1), body temperature decreased (1), electroencephalogram abnormal (1)
Metabolism and nutrition disorders (8)	anorexia (1), dehydration (3), thirst (1), oral intake reduced (2), oxygen saturation decreased (1)

System Organ Class	Preferred Terms (*n*)
Musculoskeletal and connective tissue disorders (5)	limb injury (1), muscle rigidity (2), muscle twitching (1), tibia fracture (1)
Nervous system disorders (80)	*Seizure related (24)*: convulsion (18), febrile convulsion (5), petit mal epilepsy (1)
	All others (56): abasia (1), anoxic encephalopathy (5), apnea (1), balance disorder (1), coma (5), coordination abnormal (2),depressed level of consciousness (5), dizziness (1), dystonia (1), dysarthria (1) encephalopathy (1), headache (1), hyperaesthesia (1), hypotonia (1), lethargy (10), logorrhea (1), loss of consciousness (2), somnolence (12), tremor (2), unresponsive to stimuli (2),
Psychiatric disorders (57)	abnormal behavior (5), agitation (4), crying (11), decreased activity (1), emotional disorder (2), fear (1), hallucination (7),insomnia (6), irritability (5), psychomotor hyperactivity (6), nervousness (2), restlessness (1), screaming (6)
Renal and urinary disorders (3)	anuria (1), dysuria (1), urinary retention (1),
Respiratory, thoracic and mediastinal disorders (14)	dyspnoea (6), lung disorder (1), pulmonary congestion (1), pulmonary edema (1), respiratory arrest (2), respiratory failure (1), respiratory disorder (1), respiratory distress (1)
Social circumstances (2)	immoble (1), victim of homicide (1)
Skin and subcutaneous tissue disorders (9)	generalized erythema (1), petechiae (1), pruritus (1), rash (1), tissue discoloration (1), urticaria (4)
Vascular disorders (5)	adrenal hemorrhage (1), cerebral ischemia (1), hematochezia (1), hypotension (1), shock (1)

A chart summary of the demographics and characteristics of the 150 pseudoephedrine cases is provided in Appendix I and summarized below.

Males represented a higher percentage (57%) than females (36%). The age range was 2 weeks to 5 years, with a median of 18 months. Fifty-five percent of the reports occurred in children less than 2 years of age; in this age group, adverse events related to overdoses (excluding accidental exposures), anoxic encephalopathy, cardiac disorders, and respiratory disorders were more commonly reported. In children 2 to 5 years of age, adverse events related to accidental exposures, depressed level of consciousness, and convulsions were more commonly reported. Among the cases that reported an indication, the majority were related to upper respiratory tract infections, including nasopharyngitis, cold, cough, congestion, rhinorrhea, and fever.

The dose and time to onset were not well documented fields in the MedWatch reports. Based on the drug name and the milliliters reported, the pseudoephedrine dose was determined in a little over half of the cases (61), excluding the accidental exposure cases. Each pseudoephedrine dose ranged from 2.25 – 150 mg, with a median of 15 mg. The time to onset was available for 89 reports, with 72 (81%) cases reporting an onset of 1 day or less; 52 (58%) of which reported an onset after the first dose. Thirty-three cases reported a pseudoephedrine blood level ranging from < 0.05 mg/L – 29.9 mg/L, with a median of 2.75 mg/L; 23 of which were supratherapeutic.

Therapeutic pseudoephedrine blood concentrations are considered less than 1 mg/L, with lethal levels above 10 mg/L.[18]

Of the 150 cases, 106 (71%) were associated with the use of an OTC product containing pseudoephedrine and 19 were associated with a prescription product; in the remaining 25 cases it was unspecified. Fifteen cases (10%) reported the use of a single ingredient pseudoephedrine product and 75% involved a multi-ingredient cough and cold product; in the remaining cases it was unknown. The brand name of the product was provided in 125 of the 150 cases. The most commonly reported pseudoephedrine containing product was PediaCare Infant's Decongestant and Cough drops. Five of the 125 cases reported the concomitant use of more than one cough and cold product containing pseudoephedrine. Forty-six of 150 cases reported the concomitant use of other medications, excluding multiple ingredient cough and cold products.

Forty-three (29%) of the cases reported a death outcome; 26 of which were discussed in a previous DDRE review.[1] The causes of death in these 26 cases were drug intoxication (5), multiple drug intoxication (4), death related to acetaminophen (1), cardio-respiratory arrest (1), SIDS (2), and unknown (13). The remaining 17 death cases are discussed in this review. Fourteen of the 17 new death cases were reported from the Journal of Forensic Sciences and involved children age 16 months and younger.[19] Drug intoxication was considered the cause of death or a contributory factor in all 17 cases. Among the 107 cases that did not result in death, the reported outcomes were life-threatening event (1), hospitalization (27), and other (79).

The event date was not well documented; therefore, the received date was used to evaluate the reporting trend. The number of reports of serious adverse event reports in children less than six years of age associated with pseudoephedrine received by the Agency increased approximately 2.5-fold, from 26 reports in 2002 to 63 reports in 2006. The 17 reports from 2007 are not representative of the total number of reports for the year 2007 since the data was collected midyear. The majority of the cases were reported by consumers (68%) and submitted as expedited 15-day reports (89%).

Overdoses, nervous system disorders, cardiac disorders, and respiratory disorders are discussed in more detail below. Cases may be included in more than one category.

Drug Overdose (n=74)[20]

Seventy-four cases reported adverse event terms related to a drug overdose. The cases were analyzed for manner of overdose and were further grouped into the following categories: accidental exposure (32), intentional exposure (2), medication error (8), use of multiple cough and cold preparations (5), and undeterminable (27). Of the 74 cases, 36 cases reported a death outcome, 9 cases reported hospitalization, and 29 cases were medically significant.

Most (54%) of the cases involved the use of an OTC cough and cold pseudoephedrine containing product; however, 11 cases involved the use of a prescription pseudoephedrine product and in the remaining 23 cases, the product classification was unknown. Eleven of the 74 cases reported the

[18] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

[19] Wingert WE, Mundy LA, Collins GL, Chmara ES. Possible Role of Pseudoephedrine and Other Over-the-Counter Cold Medications in the Deaths of Very Young Children

[20] The preferred terms (PT) for these cases were coded as accidental drug intake by child, accidental exposure, drug dispensing error, drug level above therapeutic, drug toxicity, incorrect dose administered, medication error, multiple drug overdose, overdose, pharmaceutical product complaint, toxicologic test abnormal, and wrong drug administered.

use of a single ingredient pseudoephedrine product; of which nine cases involved an accidental exposure, none resulting in a fatal outcome. In the remaining 2 of 11 cases, one case reported a fatal overdose involving a 2 year old; the manner of overdose was undeterminable. The product was reported as 12 Hour Pseudoephed (dose and frequency unknown) and no other information was provided. The second case reported a fatal outcome in a 4 month old infant born prematurely (34-week gestation). Pseudoephedrine was reported as the only suspect medication and no other concomitant medication was reported. The cause of death was reported as Sudden Unexpected Infant Death Syndrome (SUIDS) with pseudoephedrine blood level of 0.22 mg/L. The reporters stated that a contribution from the drug could not be ruled out.

The **accidental exposure** cases involved mostly children 2 years of age and older (24/32; 75%). Among the 32 cases of accidental exposures, 31 cases reported an accidental ingestion by the child and one case reported an accidental administration by the parent. The adverse events associated with accidental exposures included lethargy, vomiting, hyperactivity, somnolence, dilated pupils, increased heart rate, increased BP, EKG abnormality, increased/decreased respiration, hallucination, and irritability/emotional disturbance. One case of accidental exposure resulted in a death outcome and postmortem pseudoephedrine blood level was reported as 29.9 mg/L.

Two cases reported an **intentional overdose** by a caregiver. The first case reported cardio-respiratory arrest as a result of malicious overdose with pseudoephedrine blood level of 16.2 mg/L. The second case was reported as a homicide caused by pseudoephedrine toxicity with pseudoephedrine blood level of 3.4 mg/L.

Eight cases reported a **medication error**, six of which involved a prescription cough and cold product. The reported type of errors included dispensing error (3), prescribing error (1), administration error (2), and wrong drug administered (2). Three cases reported a dispensing error by the pharmacist. The pharmacist incorrectly labeled the bottle with higher dosing information resulting in hospitalization (2) and death (1). The adverse events reported in these cases were febrile seizures, unspecified cardiac adverse event, and sudden infant death syndrome. The 4th case reported incorrect prescribing by the physician resulting in somnolence, agitation and insomnia; however, no intervention or outcome was reported. The 5th and 6th cases reported incorrect drug administration by the parent or caregiver; of which one resulted in a fatal outcome with pseudoephedrine blood level of 10 mg/L and the other case reported twitching which resolved after discontinuation of the product. The 7th and 8th cases reported that the patient erroneously received the wrong drug; of which one case reported the use of a children's cough and cold preparation instead of an infant's formula and the other case involved an opiate containing cough and cold product that was intended for the patient's father and resulted in death.

Five cases reported the **use of multiple cough and cold products**; of which four resulted in a fatal outcome and one resulted in an ER visit. The five cases reported therapeutic error involving the use of two or more OTC cough and cold products containing pseudoephedrine (3); use of multiple prescription cough and cold products containing pseudoephedrine (1); and use of combination OTC and prescription cough and cold product containing pseudoephedrine (1). One case resulting in an ER visit reported that the child was given two different OTC cough and cold medications by two different caretakers. In the remaining four fatal cases the cause of death was reported as mixed drug intoxication, acute anoxic encephalopathy with undetermined drug poisoning as a contributing factor, related to acetaminophen intoxication and unknown. Postmortem pseudoephedrine blood level were reported as 10 mg/L, 1 mg/L, 3.73 mg/L, and 6.8 mg/L, respectively.

In the remaining 27 cases the manner of drug overdose was unknown. These cases involved mostly children less than 2 years of age (23/26; 88%). Eight cases involved children born

prematurely (between 27 and 37 week gestation) with ages ranging from 2 months to 6 months. Due to limited information, pseudoephedrine dose could not be determined in any of the cases. Twenty-six of the 27 cases resulted in a fatal outcome and one resulted in hospitalization. Among the 26 fatal cases, postmortem pseudoephedrine blood levels were reported in 21 of the cases, with a range of < 0.05 mg/L – 17 mg/L, and a median of 1.9 mg/L. In eight of the 26 cases, the cause of death was reported as overdose (3), acute multiple drug intoxication (3), and drug poisoning associated with pseudoephedrine as the predominant suspect drug (2). One of 26 cases may have been an overmedication based on the dosing direction and amount of drug remaining in the bottle, although it was not coded as a medication error; postmortem pseudoephedrine blood level was reported as 1.8 mg/L and the cause of death was classified as complications of minor respiratory infection and medicinal drug use.

Four of the 27 cases reported the cause of death as Sudden Infant Death Syndrome (SIDS); however, in all cases either multiple drug intoxication was detected or the sudden death was associated with drug intoxication. Five other cases reported the cause of death as congenital heart disease (1), pneumonia (1), and anoxic encephalopathy (3); however, drug intoxication was reported as a contributing factor. In the remaining eight fatal cases, the cause of death was unknown; however, one case reported that pseudoephedrine drug toxicity played a significant role in the infant's death and the pseudoephedrine blood level was 17 mg/L. The one non-fatal case reported seizures in a 5-year-old child after taking Triaminic Cough and Sore Throat tablets for a cough. This patient was hospitalized and an unspecified blood work revealed "toxicity in his system caused by an overdose of cold medications". The concomitant medication use, the outcome, and the treatment for the events were not reported.

In summary, nearly half (74/150;49%) of the cases with a serious outcome associated with pseudoephedrine in children less than 6 years of age reported an adverse event term related to a drug overdose. Most (54%) of the cases implicated the use of an OTC product. Medication errors and the use of multiple cough and cold products were contributing factors in about 18% of the cases and an accidental exposure represented a significant number of cases (43%), especially in children 2 years of age and older. In about 35% of the cases, the manner of overdose was unknown and the majority occurred in children less than 2 years of age, with eight cases involving an infant born prematurely. Drug intoxication was reported as a contributing factor in all of these 74 overdose cases.

Nervous System Disorders: Convulsion (n=24)

Twenty-four cases reported adverse event terms related to seizures coded as *convulsion (18,) febrile convulsion (5), and petit mal epilepsy (1).*

Twenty cases involved the use of an OTC cough and cold product containing pseudoephedrine, three cases involved a prescription product, and in one case the product classification was unknown. In addition to the three reports involving a prescription product, three other cases reported that the OTC cough and cold product was recommended by a healthcare provider. Nearly, all of the cases involved the use of multi-ingredient cough and cold product.

The cases involved mostly children 2 years of age and older (15/24; 63%). Eighteen of the 24 cases reported a pseudoephedrine daily dose ranging from 3.75 mg – 300 mg, with a median of 15mg. Of note, the 300 mg daily dose was due to a medication administration error that resulted in five times the prescribed daily dose. Time to onset was reported in 13 of the cases and ranged from 1 dose to 5 months, with 10 cases reporting an onset of ≤ 1 day. Of the 24 cases, nine cases reported the concomitant use of other products to include lamotrigine, oxcarbazepine, Motrin, Tylenol, unspecified antibiotic, Zyrtec, Anaprox, Amoxicillin, Viaxin, and multivitamins. Two cases also reported the concomitant use of other cough and cold products.

Four cases reported a drug overdose. The manner of drug overdose reported in these 4 cases included medication error (1), wrong drug administration (1), use of multiple cough and cold products (1), and unknown (1). One case reported seizures following the use of one or more cough and cold product for greater than 10 days. The 2nd case described seizures in a 5-year old child after being given 75 mg pseudoephedrine for one day for a cough. Unspecified blood work revealed "toxicity in his system caused by an overdose of cold medications". Concomitant medication use was unknown. The patient was hospitalized and the outcome and treatment for the events were not reported. The 3rd case described a 3 month old patient, born 3 weeks premature, treated with an unspecified pseudoephedrine and dextromethorphan product. The parents admitted to giving the infant a medication prescribed for an older sibling. The patient was admitted to the ER and found to be febrile with tachycardia and hypotension. Concomitant medication included Viaxin. The patient was given phenytoin in an attempt to control seizures. The cause of death was reported as pneumonia; however, the reporters concluded that the pseudoephedrine intoxication played a significant role in the infant's death, with postmortem pseudoephedrine blood level of 9.6 mg/L. The 4th case involving a drug administration error reported that a patient erroneously received extremely high doses of pseudoephedrine (300 mg pseudoephedrine per day) for 45 days; however, the time to onset was reported as five months after the error was detected.

Nine of the cases were confounded with a prior history of seizures (2) and fever (7). Two cases involved patients with a history of seizure disorder. One case reported an increase in the frequency of seizures two days following the administration of an OTC cough and cold preparation (30 mg pseudoephedrine per day) for nasal congestion as recommended by the pediatrician. The patient was being treated with oxcarbazepine for seizures; baseline seizure frequency was not provided. The second case did not report an indication for use but reported that seizures occurred three hours after a dose of Children's Tylenol Cold & Cough product (15 mg pseudoephedrine). According to the parents, the neurologist believed a drug interaction between pseudoephedrine and lamotrigine resulted in toxic levels; however, no drug levels were reported.

Of the seven cases confounded by the fever, five were reported as **febrile convulsions** with fever ranging from 101.7° F to 103.5 ° F. Four cases reported an onset of seizures after one dose of pseudoephedrine, with doses ranging from 3.75 mg to 11.25 mg. One case resulted in a fatal outcome and is described in more detail below. The case involving seizures after a one time dose of 3.75 mg was confounded with the concomitant administration of Tylenol and Motrin. The 5th case reported febrile seizures the same evening or the day after taking an OTC cough and cold product (dose and frequency unspecified). The 6th case involved a patient with a history of febrile seizures and it was believed that the seizures were related to the dye in the cough and cold product. The 7th case reported very high temperature of 105° F and per reporter seizure was believed to be related to the fever.

A representative case is as follows:

- An 18 month old infant experienced seizures following two dropperful of Concentrated Infants' Tylenol Cold Plus (15 mg pseudoephedrine) one time for the treatment of a fever as recommended by the pharmacist. It was reported that the patient had a slight fever. Five minutes after taking the medication the infant had a seizure, developed hives and became limp. The infant was taken to the emergency room and died of cardiac arrest. The infant had no history of epilepsy or febrile seizure. No concomitant medications were reported. The father reported that his son had taken the exact same product before without any problems. An examination of the product did not reveal any evidence of product tampering or quality problems.

The remaining 11 cases did not report any confounding factors except the concomitant use of unspecified antibiotic (1), amoxicillin (1), and multivitamins (1). Time to onset was reported as less than 1 day in five cases, of which three were after a single dose of pseudoephedrine 15 mg. The daily dose was available in six cases and ranged from 9 mg to 45 mg pseudoephedrine. One case reported a positive rechallenge whereby the patient experienced seizures on two different occasions following the administration of Triaminic Cough and Sore Throat (15 mg pseudoephedrine per dose). The product was discontinued and the events have resolved. One case resulted in hospitalization and according to the neurologist the seizures were caused by the OTC cough and cold medication. One representative case is described below:

- **Petit mal seizure** was reported in a 2 year old child, with no prior history of seizure disorder. The patient was on an unspecified antibiotic and Rondec-DM syrup one half teaspoonful twice a day (45 mg pseudoephedrine per day) for a cold. The child experienced seizures at an unknown period of time after Rondec-DM was initiated, which included collapsing, eyes rolling to the back of her head, mouth drooping and becoming unresponsive for about 1 minute. The electroencephalogram indicated normal results and the physician referred to the symptoms as "absence seizures". The mother stated that "the same events occurred on two other occasions when the cough and cold medication was given". Rondec-DM was discontinued and the absence seizures subsequently resolved.

In the above 24 cases, the outcomes were reported as hospitalization (9), death (2), and medically significant (13); of which three reported an ER visit. The two fatal cases occurred in children less than 2 years of age.

In summary, convulsions have been reported with the administration of cough and cold medications containing pseudoephedrine. Convulsions were more commonly reported in children 2 years of age and older and were all associated with multi-ingredient products. In cases where a daily dose was provided, most (89%) did not exceed the maximum recommended pseudoephedrine daily dose of 60 mg. Approximately, 17% of the cases involved a drug overdose and 38% of the cases were confounded by a history of seizure or fever. However, among the non-overdose cases, there was a strong temporal association and thus the contributory role of pseudoephedrine could not be ruled out.

Nervous System Disorders: Depressed level of consciousness (n=22)

Twenty-two cases reported adverse event terms related to depressed level of consciousness coded as *coma (5), depressed level of consciousness (5), lethargy (10), listless (4), loss of consciousness (2), somnolence (12), and unresponsive to stimuli (2).*[*]

Of the 22 cases, 17 involved the use of an OTC cough and cold product, of which two cases reported that the OTC cough and cold product was recommended by a healthcare provider. Two of 22 cases involved the use of a prescription product, and in the remaining 3 cases, the product classification was unknown. Thirteen of 22 cases involved the use of a multi-ingredient product, four cases involved the use of a single ingredient product, and in five cases it was unknown. Most of the cases involved a combination product containing an antihistamine and/or dextromethorphan.

Majority (64%) of the cases involved a child 2 years of age and older. Of the 22 cases, 17 cases also involved a drug overdose. The method of overdose reported in these cases included an accidental exposure (10), the use of multiple cough and cold products (2), a medication error (1), and unknown (4). The reported events in these overdose cases included coma, loss of

[*] Each case may have reported more than one adverse event term.

consciousness, depressed level of consciousness, unresponsive to stimuli, lethargy, and somnolence.

The remaining five cases that were not coded with a drug overdose reported the following adverse events, depressed level of consciousness (1), lethargy (2), and somnolence (2). The pseudoephedrine dose was available in four of the cases and ranged from < 3.75 mg to 15 mg. In three of the case, the time to onset was reported after one dose (2) and two doses (1). One case described a positive rechallenge in a 2 month old infant. The infant received less than 3.75 mg of pseudoephedrine five to six times a day and would experience somnolence after each dose. The patient would recover after each incident without any reported intervention.

Four of 22 cases reported the concomitant use of other products to include Tylenol (2), amoxicillin (1), and Motrin (1). Four other cases also reported the concomitant use of other cough and cold products. In the majority (68%) of the cases the outcome was reported as medically significant, of which seven resulted in an ER visit. Three cases reported hospitalization, and four cases reported a death outcome. The four fatal cases were all related to a drug overdose and involved children less than 2 years of age. The death cases reported coma (1), loss of consciousness (1), depressed level of consciousness (1), and unresponsive to stimuli (1). Postmortem pseudoephedrine levels were 3.3 mg/L, 0.67 mg/L, 2.2 mg/L, and 17 mg/L, respectively. The specific brand name of the drug product was unspecified in all four cases; however, multiple cough and cold products were involved to include, phenylpropanolamine, ephedrine, carbinoxamine, and dextromethorphan.

In summary, depressed level of consciousness, lethargy and somnolence were reported with the administration of cough and cold medicines containing pseudoephedrine. The majority (64%) of the cases involved children greater than 2 years of age. Most (59%) of the cases involved the use of a multi-ingredient cough and cold product containing either an antihistamine and/or dextromethorphan. The majority (77%) of the cases were as a result of a drug overdose to include the fatal cases. In the five cases that were not coded for a drug overdose, doses were available in four cases and were below the maximum recommended daily dose of 60 mg. These cases also reported a temporal association with one case reporting a positive rechallenge.

Nervous System Disorders: Anoxic Encephalopathy (n=6)

Six cases reported anoxic encephalopathy as an adverse event. The trade name was unknown in all six cases, and therefore, the use of a single ingredient pseudoephedrine product versus a multi-ingredient product could not be discerned. All six cases reported a fatal outcome involving a child less than 2 years of age. Three of six cases involved a drug overdose. The cause of death in the three cases was report as drug poisoning, with pseudoephedrine considered the predominant suspect drug (1), and a contributing factor (2). Postmortem pseudoephedrine blood levels were 7.1 mg/L, 1.0 mg/L, and 0.96 mg/L, respectively.

In two other cases, the contributory role of pseudoephedrine in the fatal outcome could not be ruled out. The two cases involved a 6 month old and a 2 month old infant born prematurely. The administered pseudoephedrine product, dose, frequency and indication were unknown. The cause of death was reported as anoxic encephalopathy with the manner as undetermined in both of the cases. The postmortem pseudoephedrine blood levels were 0.44 mg/L and 0.23 mg/L, respectively. The last case reported the cause of death as natural SUID possibly related to co-sleeping., with postmortem pseudoephedrine blood level of 0.30 mg/L. In 3 of 6 cases, the concomitant use of other cough and cold ingredients were reported, and in two other cases, the concomitant use of acetaminophen was reported.

In summary, all six fatal cases of anoxic encephalopathy were literature reports from the Journal of Forensic Sciences and involved children less than 2 years of age, of which 3 cases involved a

drug overdose. Little information is available about the implicated drug products containing pseudoephedrine. However, with the exception of one case, the cough and cold products were considered either the cause of death or a contributing factor. Of the six cases, 5 cases reported postmortem pseudoephedrine blood levels less than or equal to 1 mg/L.

Cardiac Disorders (n=21)

Twenty-one cases reported adverse events related to a cardiac event coded as *cardiac arrest (3), cardiac disorder (3), cardiac failure (1), cardio-respiratory arrest (4), asystole (1), cyanosis (1), myocarditis (1), electrocardiogram abnormal (1), heart rate increased (8), supraventricular tachycardia (2), and tachycardia (2).*[*]

Of the 21 cases, 11 involved the use of an OTC cough and cold product, two involved a prescription product and in eight cases the product classification was unknown. Fourteen of the 21 cases reported the use of a multi-ingredient product, one reported a single ingredient, and in the remaining six cases it was unknown.

The majority (76%) of the cases involved children less than 2 years of age. Eleven of the 21 cardiac cases involved a drug overdose. The manner of drug overdose reported in these cases included accidental exposure (4), intentional exposure (2), use of multiple cough and cold products (2), and medication error (3). The reported events in these overdose cases included cardiac disorder, cardiac arrest, cardio-respiratory arrest, tachycardia, and electrocardiogram abnormal. Of the overdose cases, five reported the concomitant use of other medications to include amoxicillin (1), senna (1), Viaxin (1), sodium chloride (1), and Tylenol (1). Two cases also reported the concomitant use of other cough and cold drugs to include guaifenesin dextromethorphan, phenylpropanolamine, and Infant Tylenol Cold.

Six cases reported **cardio-respiratory arrest**, of which five were as a result of a drug overdose. The pseudoephedrine dosage in these overdose cases was unknown. The 6th case reported cardiac arrest involving an 18 month old infant who received one dose of concentrated Infants' Tylenol Cold Plus (15 mg pseudoephedrine) for the treatment of a fever. Five minutes after taking the medication the patient developed seizures, hives, and became limp and eventually experienced cardiac arrest in the ER. The patient was not on any other concomitant medication. The infant had no history of epilepsy or febrile seizure. The father reported that his son had taken the exact same product before without any problems. Examination of the product did not reveal any evidence of product tampering or quality problems.

Three cases were unlikely related to a cough and cold product. Two of the fatal cases reported **myocarditis** and **asystole** and were unlikely related to the drug. The reported cause of death was natural myocarditis and SUID, respectively. One case resulting in hospitalization reported a **cardiac disorder** ("two small holes in the heart") which was most likely unrelated to pseudoephedrine use.

Ten cases reported tachycardia, **supraventricular tachycardia** or **increased heart rate**. Four cases resulted from a drug overdose to include one fatal case. In the remaining six cases that did not involve a drug overdose, the time to onset was available in five cases and ranged from one dose to 1 day. The pseudoephedrine daily dose was available in four of the cases and ranged from 3.75 mg to 60 mg. In four of the cases it was reported that the patients had fever and two cases reported the concomitant use of acetaminophen. Two representative cases are described below:

- A 2 week old infant reported **cardiac failure** and **supraventricular tachycardia** immediately after being given an unspecified amount of Infant PediaCare decongestant for congestion as

[*] Each case may have reported more than one adverse event term.

recommended by the physician. The patient was treated with digoxin and an unspecified medication and the symptoms resolved. The patient had no significant past medical history and was not on any concurrent therapy.

- A 2 month old infant received a dose of Infant's PediaCare decongestant Cough Drops (3.75 mg pseudoephedrine) once and experienced a heart rate of 240 bpm. The infant was taken to the hospital and received an unspecified medication for the increased heart rate, a nasogastric tube was used for feeding and an unspecified antibiotic was administered. The child was released after seven days with the events resolved. No other information regarding any past medical history or concurrent medications was provided.

In these 21 cases, the outcome was reported as death (9), hospitalization (5), and medically significant (7).

In summary, the majority of these cases (79%) involved children less than 2 years of age. In nearly half of the cases, drug overdose may have been a contributing factor. In cases that were not reported as a drug overdose, five cases reported doses that were below the maximum recommended pseudoephedrine daily dose of 60 mg. One fatal case reported cardiac arrest and the contributory role of pseudoephedrine could not be ruled out. Among the cases that reported tachycardia it is plausible that the patients experienced drug induced tachycardia based on the sympathomimetic activity of these drugs and the temporal association. Three of the 21 cases were unlikely related to a cough and cold product.

Respiratory Disorders (n=14)

Fourteen cases reported adverse events related to respiratory disorders coded as *dyspnoea (6), lung disorder (1), pulmonary congestion (1), pulmonary edema (1), respiratory arrest (2), respiratory failure (1), respiratory disorder (1), respiratory distress (1), and respiratory rate increased (5).*[*]

Of the 14 cases, eight cases involved the use of an OTC cough and cold product, three involved a prescription product, and in three cases the product classification was unknown. Ten of the 14 cases reported the use of a multi-ingredient product, two reported the use of a single ingredient product, and in the remaining two cases it was unknown.

The majority (93%) of the cases involved children less than 2 years of age. Ten of the 14 cases involved a drug overdose. The manner of drug overdose reported in these cases included accidental exposure (4), use of multiple cough and cold products (1), medication error (2), and unknown (3). The reported events in these overdose cases included dyspnea, lung disorder, respiratory arrest, respiratory failure, pulmonary edema, and pulmonary congestion.

Of the remaining four cases not coded with a drug overdose, three cases reported dyspnea and respiratory disorder after one day of receiving an OTC cough and cold product. The 1st case involving a 15 month old infant reported dyspnea after one day of receiving Infant's PediaCare Decongestant & Cough (15 mg pseudoephedrine every 4 hours). The 2nd case involving a 30 month old child reported respiratory disorder after one day of receiving Triaminic Cold & Cough (15 mg pseudoephedrine every 4-6 hours) for an unknown indication. The outcome or interventions were not reported in either of the cases. The 3rd case reported dyspnea with a fatal outcome; however, the cause of death was reported as meningitis or trauma to the head. It cannot be determined if dyspnea was related to pseudoephedrine use or underlying disease. The last case reported respiratory distress in a 2 month old infant. The patient had a history of GERD and experienced acid reflux one hour after being given Infant's PediaCare product and was taken to

[*] Each case may have reported more than one adverse event term.

the emergency room. According to the consumer, the ER physician thought the decongestant in the product acted like "speed" and caused respiratory distress.

Five of 14 cases reported the concomitant use of other medications to include amoxicillin, an unspecified antibiotic, lansoprazole, metoclopramide, and acetaminophen. Three cases also reported the concomitant use of other cough and cold drugs to include dextromethorphan, brompheniramine, ephedrine, and carbinoxamine. In the 14 cases, the outcome was reported as death (7), hospitalization (2), and medically significant (5).

In summary, respiratory adverse events have been reported with the administration of pseudoephedrine containing products. A majority (93%) of the cases involved children less than 2 years of age and 71% occurred in the context of overdose or medication error. Of the four cases that were not coded for a drug overdose, two cases were confounded by underlying disease and there is limited information in all four to determine a causal association.

3.2.2 Chlorpheniramine

An AERS search for reports of pediatric serious adverse events associated with chlorpheniramine from the past five years (1/1/2002 – 5/11/2007) retrieved 63 unique domestic spontaneous cases. The reported adverse events in the cases were categorized according to the AERS system organ class (SOC) as listed below *(a report may contain more than one adverse event term)*:

System Organ Class	Preferred Terms (*n*)
Blood and lymphatic system disorders (2)	eosinophilia (1), thymus disorder (1)
Cardiac disorders (9)	cardiac disorder (1), cardio-respiratory arrest (4), heart rate increased (3), pulse abnormal (1)
Congential, familial and genetic disorders (1)	arteriovenous malformation (1)
Endocrine disorders (3)	diabetes insipidus (2), hyperglycaemia (1)
Eye disorders (6)	eye rolling (2), mydriasis (4)
Gastrointestinal disorders (9)	abdominal strangulated hernia (1), nausea (2), vomiting (6)
General disorders and administration site conditions (20)	abasia (1), cold sweat (1), condition aggravated (3), dizziness (1), drug ineffective (1), generalised oedema (1), headache (1), hyperhidrosis (1), hypothermia (1), no therapeutic response (1), pain (1), pharmaceutical product complaint (2), pyrexia (1), sluggishness (1), swelling (1), thirst (1), unevaluable event (1)
Immune system disorder (11)	angioedema (1), drug hypersensitivity (1), face oedema (1), food allergy (1), hypersensitivity (3), Stevens-Johnson syndrome (1), urticaria (3)
Infections and infestations (11)	bronchitis (2), bronchitis chronic (1), croup infectious (1), ear infection (1), otitis media acute (1), pharyngitis (1), pneumonia (3), sinusitis (1)
Injury, poisoning and procedural complications (35)	accidental drug intake by child (4), accidental exposure (4), accidental overdose (1), drug dispensing error (1), drug toxicity (5), intentional overdose (1), medication error (12), multiple drug overdose (4), overdose (2), wrong drug administered (1)

System Organ Class	Preferred Terms (*n*)
Investigations (11)	blood bicarbonate decreased (1), blood glucose decreased (1), blood glucose increased (1), blood pH decreased (1), body temperature decreased (1), drug level above therapeutic (1), drug level increased (1), electrocardiogram abnormal (1), toxicologic test abnormal (2), white blood cell count increased (1)
Metabolism and nutrition disorders (1)	dehydration (1)
Musculoskeletal and connective tissue disorders (1)	muscle rigidity (1)
Nervous system disorders (56)	*Seizure related (17)*: convulsion (11), febrile convulsion (2), grand mal convulsion (3), simple partial seizures (1)
	All others (39): anoxic encephalopathy (2), brain death (1), brain herniation (1), brain oedema (1), brain stem infarction (1), cerebral infarction (1), cerebrovascular accident (1), coma (5), confusional state (1), coordination abnormal (1), disorientation (1), dystonia (1), hydrocephalus (1), hypersomnia (1), insomnia (1), lethargy (8), loss of consciousness (1), psychomotor hyperactivity (2), restlessness (2), somnolence (3), tremor (2), unresponsive to stimuli (1)
Pregnancy, puerperium and perinatal conditions (3)	infantile spitting up (1), neonatal disorder (1), poor weight gain neonatal (1)
Psychiatric disorders (13)	abnormal behaviour (1), aggression (1), agitation (1), anxiety (1), crying (3), emotional distress (1), hallucination (1), hallucination-visual (2), screaming (1), sleep disorder (1)
Renal and urinary disorders (1)	urinary incontinence (1)
Respiratory, thoracic, and mediastinal disorders (20)	alveolitis (1), asthma (1), cough (2), cyanosis (3), dyspnoea (4), hyperventilation (1), lung disorder (1), pleural disorder (1), respiration abnormal (1), respiratory depression (1), respiratory depth increased (1), respiratory disorder (1), rhinorrhoea (1), throat tightness (1)
Skin and subcutaneous tissue disorders (7)	eczema (1), pallor (1), petechiae (1), pruritus (1), rash (1), rash macular (1), rash pruritic (1)
Social circumstances (4)	treatment noncompliance (1), victim of homicide (3)
Vascular disorders (3)	hypertension (1), hypotension (1), shock (1)

A chart summary of the demographics and characteristics of the 63 chlorpheniramine cases is provided in Appendix II, and summarized below.

Males represented a higher percentage (63%) than females (35%). The age range was 1 month – 5 years, with a median of 2 years. The majority of the cases (65%) were reported in children 2 to 5 years of age. Among the cases that reported an indication, the majority (36%) were upper respiratory tract infections or symptoms of respiratory tract infections, including nasopharyngitis, cold, cough, congestion, rhinorrhea, and fever.

The dose and time to onset were not well documented in the reports. Based on the drug name and the milliliters reported, each dose of chlorpheniramine was determined in 32 cases (51%); ranging from 0.05 – 12 mg, with a median of 1 mg. The time to onset was available for 36 of the reports, where approximately 50% (20) reported an onset after the first dose and 75% (27) reported an onset within the first day. Six cases reported a chlorpheniramine postmortem blood level ranging

from 0.04 mg/L – 0.21 mg/L, with a median of 0.07 mg/L; all of which were above the therapeutic range. One case that reported a blood level of "< 0.25 mg/L" was excluded because an exact number was not provided. Chlorpheniramine therapeutic blood concentrations range from 0.01 – 0.02 mg/L.[21] There are limitations to accurately interpreting postmortem levels of chlorpheniramine, especially considering its potential for redistribution following death; therefore, the reported drug levels cannot be used as definitive data in attempting to predict antemortem concentrations, but rather as support for known clinical findings.[22,23]

Of the 63 cases, 35 (56%) were associated with an OTC product containing chlorpheniramine and 20 (32%) were associated with a prescription product; in the remaining 8 cases it was unspecified. None of the cases reported a single ingredient chlorpheniramine product and 55 (87%) involved a multi-ingredient product; in the remaining 8 cases it was indeterminable. The trade name of the primary cough and cold product was reported in 54 of 63 cases. The most frequently reported product was Tussionex ER suspension (8), a prescription product that contains hydrocodone and chlorpheniramine. The next four most frequently reported products were OTC cough and cold medications, including PediaCare Children's Nightrest Cough & Cold (7), Triaminic Cold & Cough liquid (7), PediaCare Children's Multi-Symptom Cold liquid (5), and Triaminic Cold & Night Time Cough liquid (4).

Thirty-two cases reported concomitant medications; 13 of which reported the concomitant use of more than one cough and cold medication and 27 cases reported the concomitant use of other medications excluding cough and cold products. Approximately 30% (20) of the cases reported a death outcome; 16 of which were discussed in a previous DDRE review[1] and the causes of death were reported as follows: overdose-6, cardio-respiratory arrest-4, multiple drug overdose-1, subarachnoid hemorrhage-1, and unknown-4. The remaining 4 death cases will be discussed in this review. Among the 43 cases that did not result in death, 16 reported a hospitalization, 1 reported a life-threatening event, and the remaining 26 cases reported "other."

The event date field was not well documented; therefore, the received date was used to evaluate the trend. Based on the date of the reports received by the Agency from 2002 to 2007, the number of reports peaked in 2003 (19) and appears to be trending down; however, there was a slight increase in reports from 2005 (8) to 2006 (11). The three reports for 2007 are not representative of the total number of reports for the year 2007 since the data was collected mid-year. The majority of cases were reported by consumers (74%) and were submitted as expedited 15-day reports (91%).

Overdoses, nervous system disorders, cardiac disorders, and respiratory disorders are discussed in more detail below. Cases may be included in more than one category.

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[21] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

[22] Leikin JB, Jerrold B, Watson WA, William A. Post-mortem toxicology: What the dead can and cannot tell us. J of Toxicology. 2003;41(1): 47-56.

[23] Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. J Clin Pathol, 2000;53(4):282-5.

Drug Overdose (N=31)[24]

Thirty-one cases reported adverse event terms related to a drug overdose. The cases were analyzed for manner of overdose and were further grouped into the following categories: accidental drug intake by a child (12), medication errors (10), intentional poisoning by a caregiver (5), pharmaceutical product complaint (1), and indeterminable (3). Over 50% (16) of the cases reported a death outcome, 17 cases reported a hospitalization and of the remaining 30 cases that were medically significant, 11 reported an ER visit.

Twenty-three of 31 (74%) cases were reported in children 2 to 5 years of age. Twenty-two of 31 cases reported the use of concomitant medications; 10 of which involved the use of more than one antihistamine-containing product. Of the 31 cases, 23 reported a multi-ingredient cough and cold product, no cases reported a single ingredient chlorpheniramine product, and in the remaining 8 cases it was indeterminable. Fourteen cases reported the use of an OTC chlorpheniramine product, 10 reported a prescription product, and in the remaining 7 cases it was unknown.

Twelve cases reported an **accidental drug intake by a child**. Eight of 12 cases reported neurologic adverse events including brain death-1, brain herniation-1, brain stem infarction-1, cerebral infarction-1, coma-2, coordination abnormal-1, lethargy-3, psychomotor hyperactivity-1, somnolence-1, and unresponsive to stimuli-1. Two of 12 cases reported respiratory adverse events including dyspnea-1 and cardio-respiratory arrest-1, and 2 cases reported cardiac adverse events including cardio-respiratory arrest-1 and heart rate increased-1. Two cases did not report an adverse event. Of the 12 cases, 4 reported a death outcome. The cause of death was reported as cardio-respiratory arrest in one case and unknown in the remaining 3 cases. Among the 8 that did not result in death, 4 reported an ER visit, and all were released within several hours to the next day. Treatments included observation only, activated charcoal, intravenous fluids, and Narcan.

Ten cases were categorized as **medication errors** and involved product confusion (3), incorrect drug (3), confusion between units of measurement (3), and dosing error (3). Cases may have reported more than one type of error. Two of these cases are discussed in the DMETS review[25] (ISR # 3874984 and 4755459). An example of each type of error is as follows: The 1st case involved product confusion in a 5 year old child who was prescribed Rynatan Chewable tablets (4.5 mg of chlorpheniramine/tablet) and was dispensed Rynatuss Adult tablets (5 mg of chlorpheniramine/tablet). The child received two doses before the error was discovered and experienced lethargy, drowsiness and an increased heart rate resulting in an overnight hospital stay. The 2nd case involved an improper selection of a multi-ingredient OTC cough and cold product to treat a fever (no other indications were reported); the reported adverse events were convulsion, increased heart rate, mydriasis, tremor, vomiting, increased blood glucose, eye rolling, pain and pallor. The 3rd case involved confusion between the units of measurement in a 6 month old infant who was prescribed Tussionex 0.5 mL (0.8 mg of chlorpheniramine) twice daily, but was dispensed a Tussionex bottle labeled with directions to take 0.5 teaspoons (4 mg of chlorpheniramine) twice daily. The infant received 2 doses and had respiratory depression and was hospitalized for 12 hours. The 4th case was speculated to be a dosing error where the volume remaining in a cough and cold medication was significantly less than the amount expected based

[24] The preferred terms (PT) for these cases were coded as medication error, drug dispensing error, wrong drug administered, accidental exposure, accidental overdose, accidental drug intake by child, drug level above therapeutic, toxicologic test abnormal, drug toxicity, overdose, multiple drug overdose, and intentional overdose.

[25] DMETS review of medication errors involving OTC cough and cold medications in pediatrics. In progress as of Sept 2007.

on the dose and number of doses administered. Four of 10 cases reported a death outcome and were discussed in the previous DDRE review[1]. These death cases involved an incorrect drug (1), confusion between units of measurement (1), and dosing error (2).

Five cases were categorized as **intentional poisonings** by a caregiver. All 5 cases reported a death outcome. The cause of death was reported as cardio-respiratory arrest from a multiple drug toxicity-1, acute drug toxicity-1 and multiple drug overdose-3.

One case reported a **pharmaceutical product complaint** that involved a prescription chlorpheniramine product that had been recalled for a super-potency of the active ingredients; reported adverse events were restlessness and vomiting.

The manner of overdose was **indeterminable** in 3 cases. All three cases reported a death outcome. The cause of death was reported as anoxic encephalopathy-2 and multiple drug overdose-1; however, all 3 cases were confounded by concomitant medications. One of the cases was also confounded by a previous hospital admission for pneumonia and "brain bleed." Despite the confounders, one case reported a supratherapeutic chlorpheniramine blood level of 0.07 mg/L.

In summary, deaths and serious adverse events related to the nervous, respiratory, and cardiac systems have been reported with overdoses of cough and cold medications containing chlorpheniramine, especially in children 2 to 5 years of age. Thirty-one (49%) cases that reported a neurologic, cardiac, or respiratory adverse event was likely or possibly related to the use of a chlorpheniramine-containing cough and cold product. Accidental exposures and medication errors represent a significant percentage of drug overdose cases (71%). Since the majority (74%) of reported products were multi-ingredient, the exact role of chlorpheniramine is not known; however, the contributory role of chlorpheniramine could not be ruled out.

Nervous System Disorders: Convulsion (N=14)

Fourteen cases reported adverse events related to seizures coded as *convulsion (10), febrile convulsion (2), grand mal convulsion (2), and simple partial seizures (1).*[*]

Ten of 14 cases (71%) involved children 2 to 5 years of age. The dose was calculated in 8 of the 14 convulsion cases: range 0.05 mg – 1 mg, median 0.6 mg. None of the doses exceeded the labeled dosage for the lowest age group. Eight of 14 cases reported a time to onset with a range of one dose to 10 days, with a median of one dose. Six of 14 cases reported the use of concomitant medications; 2 of which involved the use of more than one antihistamine-containing product. All 14 cases reported the use of a multi-ingredient cough and cold product. Thirteen cases reported the use of an OTC medication and one reported a prescription medication.

One of 14 cases reported a recoding of the adverse event term to "seizure-like activity".

Seven of the remaining 13 cases reported the following confounding factors: history of seizures-2, coded as febrile seizures or reported a fever-4, and long duration of cough and cold product use (>10 days)-1.

In the remaining 6 cases, no confounding factors were reported. One case denied a history of seizures. The time to onset was reported in 5 cases, ranging from 1 dose to 1 week with a median of 1 dose. The dose was reported in 3 cases, all 3 of which did not exceed the labeled dose for the lowest age group. One of the 3 cases mentioned above involved a one year old child who was administered a chlorpheniramine dose (0.05 mg) that did not exceed the lowest labeled dose; however, there are no dosing recommendations for children less than 2 years of age except to consult a physician.

[*] Each case may have reported more than one adverse event term.

None of the 14 cases reported a death outcome; 8 cases reported a hospitalization and of the remaining 6 cases that were medically significant, 3 reported an ER visit.

In summary, convulsions have been reported in association with the administration of chlorpheniramine doses that did not exceed the labeled dosage for the lowest age group. Approximately 70% of the cases reporting convulsions with chlorpheniramine involved children 2 to 5 years of age. Six (43%) of 14 cases that reported convulsions did not report any confounding factors; 3 of which reported doses that did not exceed the lowest labeled dose. Fifty percent of the cases were confounded by a history of seizure, diagnosis of febrile seizure or pneumonia, or long duration of cough and cold product use; however, the contributory role of chlorpheniramine could not be ruled out.

Nervous System Disorders: Depressed level of consciousness (N=17)

Seventeen cases reported adverse events related to a depressed level of consciousness coded as *anoxic encephalopathy (2)*, *coma (5)*, *confusional state (1), disorientation (1), lethargy (6), loss of consciousness (1)*, *somnolence (3),* and *unresponsive to stimuli (1)*.

Six cases reported the use of an OTC medication, 7 reported a prescription medication, and in the remaining 4 cases it was unknown. Of the 17 cases, 13 reported a multi-ingredient cough and cold product, no cases reported a single ingredient chlorpheniramine product, and in the remaining 4 cases it was indeterminable.

Ten of 17 cases (59%) involved children 2 to 5 years of age. Of the 17 cases, 11 cases involved a drug overdose; the manner of overdose was accidental drug intake by child (6), medication errors (2), intentional poisoning (1), and indeterminable (2). The reported events in the overdose cases included somnolence-3, lethargy-5, coma-3, anoxic encephalopathy-2, and unresponsive to stimuli-1. Two of 17 cases involved multiple drug intoxication. In these cases, a possible association between the use of pseudoephedrine and the reported events could not be ruled out.

Six cases were not coded as a drug overdose; 4 of which reported a dose. The 1st case reported a dose (2 mg) slightly above the recommended dosage for the appropriate age group. The 2nd and 3rd cases involved children less than 2 years of age; one of which reported a dose (0.5 mg) that did not exceed the labeled dosage for the lowest age group and the other slightly exceeded the labeled dosage for the lowest age group, per the monograph. The 4th case reported a high dose (8 mg) but was not coded as an overdose. The reported events in these 6 cases were lethargy-3, coma-2, confusional state-1, disorientation-1, and loss of consciousness-1. Three of 6 cases were confounded by the concomitant use of diphenhydramine-1 and other cough and cold products-2. Three of 6 cases reported a chlorpheniramine/opiate combination product. Significant past medical history included an arteriovenous malformation in one case.

Of the 17 cases, 9 cases reported a death outcome, 4 cases reported hospitalization and of the remaining 4 cases that were medically significant, 2 reported an ER visit. The causes of death for the 9 cases were reported as cardio-respiratory arrest-2, multiple drug overdose-1, anoxic encephalopathy with drug intoxication as a contributing cause-2, and unknown-4.

In summary, depressed level of consciousness was reported with the administration of cough and cold medicines containing chlorpheniramine. Over half of the cases (59%) involved children 2 to 5 years of age. Eleven (65%) of 17 cases were confounded by an overdose. The remaining 6 cases were confounded by an arteriovenous malformation, a chlorpheniramine/opiate combination product, or concomitant use of more than one antihistamine containing product; however, the contributory role of chlorpheniramine in these cases could not be ruled out.

Cardiac Disorders (N=9)

Nine cases reported adverse events related to cardiac events coded as *cardio-respiratory arrest (4), increased heart rate (3), irregular electrocardiogram (1), and an unspecified cardiac disorder (1).*

Of the 9 cases, 5 reported the use of a multi-ingredient cough and cold product, none reported a single ingredient chlorpheniramine product, and in the remaining 4 cases it was indeterminable. Two cases reported the use of an OTC medication, 3 reported a prescription medication, and in the remaining 4 cases it was unknown.

Six of 9 cases (67%) involved children 2 to 5 years of age. Eight of 9 cases involved a drug overdose. The reported events were cardio-respiratory arrest (4), heart rate increased (2), irregular EKG (1), and an unspecified cardiac disorder (1). The manner of overdose was as follows: an accidental drug intake by a child (3), medication error (3), and intentional poisoning (2). The one remaining case that was not coded as a drug overdose reported an increased heart rate.

All 4 cases that reported **cardio-respiratory arrest** involved a drug overdose (medication error-2, accidental-1, and intentional-1) and resulted in death. The 1st case involved an intentional overdose and was confounded by the use of concomitant medications (doxepin and carbinoxamine) but reported a high postmortem chlorpheniramine blood level (0.07 mcg/mL). The 2nd case involved a medication error and speculated that an overdose occurred with a cough and cold medication but provided very little information; however, the contributory role of chlorpheniramine in these 2 cases could not be ruled out. The remaining two cases that were associated with a chlorpheniramine-containing product reported a likely temporal association, lack of confounding factors, and/or a high postmortem chlorpheniramine level (0.21 mcg/mL); one of which involved a medication error where the mother may have accidentally administered the father's medication to the child since they both have the same names and they were both taking medications with similar ingredients.

Three cases reported an **increased heart rate**; two of which reported heart rates ranging from 140 to 150 bpm. The age ranged from 3 to 5 years. Two cases involved a drug overdose (medication error-1, accidental-1); one of which resulted in death. The medication error case involved confusion between two similar sounding drugs (Rynatuss and Rynatan) and resulted in a hospitalization. The accidental ingestion case reported the concomitant use of ibuprofen. The third case was unclear as to the total dose ingested and also reported a fever, which is known to increase heart rate. Despite the confounders in these 3 cases, the contributory role of the chlorpheniramine-containing cough and cold products could not be ruled out.

One case reported an **irregular EKG** (unspecified) following an accidental drug intake by a child and was treated with intravenous fluids and released after several hours.

One case reported an **unspecified cardiac disorder** that involved a drug overdose from an intentional poisoning by a caregiver, and resulted in death. The case was confounded by multiple concomitant medications (valproic acid, clonidine, chlorpheniramine, and Seroquel); however, the contributory role of dextromethorphan could not be ruled out.

In the above 9 cases, 6 cases reported a death outcome, 2 cases reported a hospitalization, and the remaining case reported an ER visit.

In summary, cardiac adverse events have been reported with the administration of cough and cold medicines containing chlorpheniramine, especially in children 2 to 5 years of age. The majority (89%) of cardiac related cases involved drug overdoses of chlorpheniramine-containing products.

The one remaining case was unclear as to whether an overdose occurred and reported an increased heart rate.

Respiratory Disorders (N=18)

Eighteen cases reported adverse events related to respiratory disorders coded as *cardio-respiratory arrest (4), dyspnoea (4), cyanosis (3), alveolitis (1), cough (1), chronic bronchitis (1), hyperventilation (1), lung disorder (1), respiratory depression (1), respiratory depth increased (1), respiratory disorder (1), respiration abnormal (1), and throat tightness (1).*

Of the 18 cases, 13 reported the use of a multi-ingredient cough and cold product, none reported a single ingredient chlorpheniramine product, and in the remaining 5 cases it was indeterminable. Five cases reported the use of an OTC medication, 8 reported a prescription medication, and in the remaining 5 cases it was unknown.

Twelve of 18 cases (67%) involved children 2 to 5 years of age. Ten of 18 cases involved a drug overdose (an accidental drug intake by a child-3, intentional poisoning-4, and medication error-3) and reported the following adverse events: cardio-respiratory arrest-4, dyspnea-2, cyanosis-2, lung disorder-1, respiratory depression-1, and respiration abnormal-1.

Four cases reported **cardio-respiratory arrest**; one of the 4 cases was also coded as **respiration abnormal**. The age ranged from 4 months to 4 years. All 4 cases involved a drug overdose (an accidental drug intake by a child-1, intentional poisoning-1, and medication error-2). All 4 cases reported a death outcome.

Four cases reported **dyspnea**. The age ranged from 2 to 3 years. Two cases involved a drug overdose (an accidental drug intake by a child-1 and intentional poisoning-1); one of which reported a death outcome and the cause of death was reported as a homicide and the other case reported an ER visit. Of the remaining 2 cases, one was confounded by the use of a combination chlorpheniramine/hydrocodone product and a chlorpheniramine dose that exceeded the recommended dosage; the 2nd case was confounded by dyspnea likely secondary to a seizure that was also reported as an adverse event. Since hydrocodone is an opiate, and opiates are known to cause respiratory depression, it is difficult to assess the contributory role of chlorpheniramine in the cases that reported the use of such products.

Three cases reported **cyanosis**. The age ranged from 2 months to 3 years. Two cases involved a drug overdose (an accidental drug intake by a child-1 and intentional poisoning-1); both of which reported a death outcome and the cause of death was reported as a drug overdose in both cases. The remaining case was confounded by cyanosis associated with a seizure was also reported as an adverse event.

One case reported **respiratory depression.** This case involved a drug overdose from a medication error where 0.5 mL of Tussionex was incorrectly dispensed as 0.5 teaspoons to a six month old infant. After two doses were administered, the patient required a hospitalization.

Four cases that reported **throat tightness**, **cough**, **hyperventilation**, and **lung disorder** were all confounded. Three of 4 cases reported a pre-existing medical condition; 2 of which were related to hypersensitivity reactions to food, and the 3rd case reported an arteriovenous malformation. The 4th case that reported an unspecified lung disorder involved a drug overdose from an intentional poisoning by a caregiver, and was confounded by a multiple drug overdose. Despite the confounders, the contributory role of chlorpheniramine in these cases could not be ruled out.

Of the remaining 2 cases that were coded as **alveolitis** and **chronic bronchitis**, or **respiratory depth increased** and **respiratory disorder**, one case reported a dose at the recommended dosage, while the other case exceeded it. The 1st case involved the death of a child who received 4 doses of Tussionex (8 mg of chlorpheniramine per dose) and an autopsy revealed chronic

inflammation of the bronchi, acute intra-alveolar inflammation, and mild cerebral edema. The 2nd case involved a 30 month old child who was administered 5 mL of Triaminic Cold & Cough (1 mg of chlorpheniramine) every 4 to 6 hours, as prescribed by a physician and developed heavy and irregular breathing. According to the report, the child had previously been exposed to the product without any adverse events.

Among the above 18 cases, 10 reported a death outcome, 5 cases reported a hospitalization and of the 3 remaining cases that were medically significant, 2 reported an ER visit.

In summary, respiratory adverse events have been reported with the use of cough and cold medications containing chlorpheniramine. The majority of cases (94%) were confounded by overdoses, pre-existing medical conditions, the use of multi-ingredient products containing an opiate, or likely a secondary event to a seizure that was also reported as an adverse event. One case reported heavy and irregular breathing following the ingestion of a recommended dosage of chlorpheniramine and did not report any confounding factors.

3.2.3 Diphenhydramine

An AERS search for reports of pediatric serious adverse events associated with diphenhydramine from the past five years (1/1/2002 – 5/11/2007) retrieved 83 unique domestic spontaneous cases. The reported adverse events in the cases were categorized according to the AERS system organ class (SOC) as listed below *(a report may contain more than one adverse event term)*:

System Organ Class	Preferred Terms (*n*)
Cardiac disorders (12)	cardio-respiratory arrest (4), heart rate increased (6), left bundle branch block (1), palpitations (1)
Eye disorders (13)	conjunctival disorder (1), eye disorder (1), eye swelling (5), eyes sunken (1), mydriasis (1), optic nerve sheath haemorrhage (1), pupil fixed (1), retinal haemorrhage (1), vitreous haemorrhage (1)
Gastrointestinal disorders (14)	abdominal distention (1), constipation (2), diarrhoea (1), dry mouth (2), faeces discoloured (1), stomach discomfort (1), vomiting (6)
General disorders and administration site conditions (29)	condition aggravated (3), dizziness (1), drug ineffective (3), drug interaction (1), fatigue (3), feeling abnormal (1), feeling drunk (1), feeling hot (1), feeling jittery (1), gait disturbance (1), generalised oedema (1), hyperhidrosis (1), inflammation (1), influenza like illness (1), malaise (1), no adverse drug effect (1), no therapeutic response (1), oedema peripheral (1), pharmaceutical product complaint (1), pyrexia (2), sudden death (1), swelling (1)
Immune system disorder (7)	angioedema (1), food allergy (1), reaction to drug excipients (1), throat tightness (1), type IV hypersensitivity reaction (1), urticaria (2)
Infections and infestations (2)	pneumonia (1), urinary tract infection (1)
Injury, poisoning and procedural complications (65)	accidental drug intake by child (10), accidental overdose (9), accidental exposure (9), contusion (2), drug level above therapeutic (2), drug toxicity (7), fall (1), intentional drug misuse (3), intentional overdose (2), laceration (1), limb injury (1), medication error (9), multiple drug overdose (2), overdose (4), poisoning (1), thermal burn (1), underdose (1)

System Organ Class	Preferred Terms (*n*)
Investigations (33)	activated partial thromboplastin time prolonged (1), alanine aminotransferase increased (1), allergy test positive (1), aspartate aminotransferase increased (2), aspiration tracheal (1), blood amylase increased (1), blood bicarbonate decreased (1), blood creatinine phosphokinase abnormal (1), blood iron increased (1), blood lactate dehydrogenase increased (1), blood pH decreased (1), blood pressure decreased (1), body temperature increased (3), drug level (1), drug level increased (1), drug screen positive (2), electrocardiogram abnormal (1), lymphocyte count increased (1), monocyte count decreased (1), PCO2 decreased (1), pulse absent (1), therapeutic agent toxicity (2), toxicologic test abnormal (6)
Metabolism and nutrition disorders (3)	anorexia (1), dehydration (1), polydipsia (1)
Musculoskeletal and connective tissue disorders (6)	muscle twitching (3), musculoskeletal stiffness (1), rhabdomyolysis (1), tibia fracture (1)
Nervous system disorders (63)	*Seizure related (7)*: convulsion (5), febrile convulsion (1), partial seizures (1) *All others (56)*: brain oedema (2), choreoathetosis (1), coma (8), confusional state (2), depressed level of consciousness (3), disorientation (2), dysarthria (1), dyskinesia (3), dysphonia (2), facial palsy (1), hyperreflexia (2), hypersomnia (1), incoherent (1), insomnia (4), lethargy (3), loss of consciousness (3), middle insomnia (1), psychomotor hyperactivity (3), restlessness (1), somnolence (9), subdural haematoma (1), syncope (1), tremor (1)
Pregnancy, puerperium and perinatal conditions (3)	neonatal apnoeic attack (1), sudden infant death syndrome (2)
Psychiatric disorders (28)	abnormal behaviour (3), aggression (1), agitation (5), anxiety (1), crying (1), euphoric mood (1), hallucination (4), hallucination-auditory (1), hallucination-visual (4), mood altered (1), nervousness (1), personality change (1), screaming (1), sleep disorder (1), staring (1), tic (1)
Renal and urinary disorders (3)	dysuria (1), polyuria (1), urinary incontinence (1)
Respiratory, thoracic, and mediastinal disorders (31)	apnoea (1), asphyxia (2), Cheyne-Stokes respiration (1), cough (2), cyanosis (3), dyspnoea (5), hypoxia (1), increased upper airway secretion (1), nasal congestion (3), productive cough (1), pulmonary congestion (1), respiratory arrest (3), respiratory rate increased (1), rhinorrhoea (2), sneezing (2), throat irritation (1), yawning (1)
Skin and subcutaneous tissue disorders (15)	dry skin (1), eczema (1), erythema (4), petechiae (1), pruritus (2), rash (1), rash erythematous (1), rash generalized (1), rash pruritic (1), skin discolouration (1), skin warm (1)
Social circumstances (7)	child abuse (1), homicide (1), victim of child abuse (1), victim of homicide (4)
Surgical and medical procedures (1)	resuscitation (1)
Vascular disorders (2)	haemorrhage (1), livedo reticularis (1)

A chart summary of the demographics and characteristics of the 83 diphenhydramine cases is provided in Appendix III, and summarized below.

Males represented a slightly higher percentage (53%) than females (42%). The age ranged from 3 weeks – 5 years, with a median of 2 years. Approximately 47% of the reports occurred in children less than 2 years of age; 30% occurred in children less than one year of age and this represented the largest age group. Many of the adverse events (drug overdoses, convulsions, depressed level of consciousness, and cardiac and respiratory disorders) occurred fairly equally in both the less than 2 years of age group and the 2 to 5 years of age group. Excluding the cases that reported accidental ingestions and accidental overdoses as indications, the most commonly reported indications were hypersensitivity reactions including allergy, hives, rash and rhinorrhea, followed by upper respiratory tract infections or symptoms of respiratory tract infections, including cold, cough, nasal congestion, sinus infection and throat infection.

The dose and time to onset were not well documented in the reports. Based on the drug name and the milliliters reported, the diphenhydramine dose was determined in approximately 34% of the cases. Each diphenhydramine dose ranged from 1 – 100 mg, with a median of 12.5 mg. The time to onset was available for 29 of the reports, where approximately 90% (25) reported an onset within 1 day, of which approximately 50% (14) reported an onset after the first dose. Fourteen cases reported a postmortem diphenhydramine blood level ranging from 0.07 mg/L to greater than 10 mg/L, with a median of 1.6 mg/L; 10 of which were supratherapeutic, one case was subtherapeutic, and the remaining 3 cases were within therapeutic range. Diphenhydramine therapeutic blood concentrations range from 0.1 – 1 mg/L.[26] There are limitations to accurately interpreting postmortem levels of diphenhydramine, especially considering its potential for redistribution following death; therefore, the reported drug levels cannot be used as definitive data in attempting to predict antemortem concentrations, but rather as support for known clinical findings.[27,28]

Of the 83 cases, 64% (53) were associated with the use of an OTC product containing diphenhydramine and none were reportedly associated with a prescription product; in the remaining 30 cases it was unspecified. The trade name of the primary cough and cold product was reported in 55 of 83 cases. The top most frequently reported trade name was Children's Benadryl Allergy Liquid (24), followed distantly by Children's Benadryl Dye Free Allergy Liquid (6). Of the 83 cases, 53% (44) involved a single ingredient diphenhydramine product and 13% (11) involved a combination cough and cold product; in the remaining 28 cases it was indeterminable. Thirty-one cases reported the use of concomitant medications; 11 of which reported the concomitant use of more than one cough and cold medications and 25 cases reported the concomitant use of other medications excluding cough and cold products. Cases may have reported more than one concomitant medication. Eleven of 83 cases reported the concomitant use of more than one antihistamine, to include Zyrtec-3, a cough and cold product containing an antihistamine-5, doxylamine-1, and chlorpheniramine-2.

Approximately 30% (26) of the cases reported a death outcome; 23 of which were discussed in a previous DDRE review[1] and reported the following causes of death: diphenhydramine

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[26] Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

[27] Leikin JB, Jerrold B, Watson WA, William A. Post-mortem toxicology: What the dead can and cannot tell us. J of Toxicology. 2003;41(1): 47-56.

[28] Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. J Clin Pathol, 2000;53(4):282-5.

intoxication (6), multiple drug toxicity (1), cardiac arrest (1), multi-organ failure (1), compressional asphyxia (1), and undetermined (13). The remaining 3 death cases reported cardio-respiratory arrest, multiple drug toxicity, and diphenhydramine toxicity as the causes of death. Among the 57 cases that did not result in death, 15 reported hospitalization, and the remaining 42 cases reported "other" as an outcome.

The event date field was not well documented; therefore, the received date was used to evaluate the trend. Based on the date of the reports received by the Agency from 2002 to 2007, the number of reports increased significantly from 2004 (8) to 2005 (30) and then dropped slightly in 2006 (22). The five reports for 2007 are not representative of the total number of reports for the year 2007 since the data was collected mid-year. The majority of cases were reported by consumers (69%) and were submitted as expedited 15-day reports (94%).

Overdoses, nervous system disorders, cardiac disorders, and respiratory disorders are discussed in more detail below. Cases may be included in more than one category.

Drug Overdose (N=46)[29]

Forty-six cases reported adverse events related to a drug overdose. The manner of overdose was as follows: accidental drug intake by a child (22), medication errors (4), accidental overdoses (4), intentional poisoning by a caregiver (11), and indeterminable (5).

Slightly over half of the cases (53%) involved children 2 to 5 years of age. Twelve cases reported the use of concomitant medications; 6 of which involved the use of more than one antihistamine-containing product. Of the 46 cases, 23 cases reported the use of a single ingredient diphenhydramine product, 4 reported a multi-ingredient cough and cold product, and in the remaining 19 cases it was indeterminable. Twenty-six cases reported the use of an OTC medication, none reported a prescription medication, and in the remaining 20 cases it was unknown.

Eighteen cases reported adverse events related to the nervous system, and included coma-7, somnolence-6, convulsion-2, loss of consciousness-2, choreoathetosis-1, confusional state-1, disorientation-1, dyskinesia-1, gait disturbance-1, hyperreflexia-1, hypersomnia-1, insomnia-1, and lethargy-1. Nine cases reported cardiac related adverse events, and included increased heart rate-4, cardiac or cardio-respiratory arrest-4, and left bundle branch block and EKG ST-T change-1. Ten cases reported a respiratory related adverse event, and included respiratory or cardio-respiratory arrest-5, dyspnea-2, apnea-1, hypoxia-1, infantile apneic attack-1, pulmonary congestion-1, and pulmonary edema-1. Cases may have reported more than one respiratory adverse event. One of the cases that reported an increased heart rate also reported rhabdomyolysis. This case was reported in the literature and involved an accidental ingestion of an unknown amount of diphenhydramine tablets. The time to onset was reported as within 4 hours. The initial creatinine kinase (CK) was 1619 U/L (normal range 24 – 195 U/L), a repeat in 9 hours was 4505 UL, and subsequent CKs on hospital days 2, 3 and 4 were 2893 U/L, 2232 U/L and 1205 U/L, respectively. The renal status remained normal, an EKG was unremarkable, and no seizures were reported during the hospital stay.

Approximately 22 (50%) of the cases reported a death outcome, 11 cases reported a hospitalization, and of the remaining 13 cases that were medically significant, 8 reported an ER visit. The majority (75%, 16) of the death cases involved children less than 2 years of age. The

[29] The preferred terms (PT) for these cases were coded as accidental drug intake by child, accidental exposure, accidental overdose, drug level above therapeutic, drug toxicity, intentional drug misuse, intentional overdose, medication error, multiple drug overdose, overdose, poisoning, and toxicologic test abnormal.

causes of death were reported as cardio-respiratory arrest (6), multi-organ system failure (1), diphenhydramine toxicity (3), overdose (2), multiple drug overdose (3), and unknown (7). Diphenhydramine blood levels were reported in 12 cases; all of which reported a death outcome, and the levels ranged from 0.8 to greater than 10 mg/L, with a median of 2 mg/L.

In summary, deaths and serious adverse events related to the nervous, cardiac, and respiratory systems, as well as other notable events such as rhabdomyolysis, have been reported with overdoses of diphenhydramine-containing products. Children less than 2 years of age accounted for approximately 50% (22) of the cases, and an even higher percentage (75%, 16) of deaths. Approximately 46% of the cases were coded as overdoses, among them the two largest percentages with respect to the manner of overdose were an accidental drug intake by a child (48%) and intentional poisoning (24%).

Nervous System Disorders: Convulsion (N=7)

Seven cases reported adverse events related to seizures coded as *convulsion (5), febrile convulsion (1), and partial seizures (1)*.

Four of 7 cases (57%) involved children 2 to 5 years of age. Three of 7 cases involved an accidental drug intake by a child. Of the remaining 4 cases, all were confounded by the following factors: pre-existing cerebral palsy (which can be associated with seizures)-1, concomitant use of antihistamines (Zyrtec and an unspecified anti-allergic medication)-2, and pyrexia-1; however, the contributory role of diphenhydramine in theses cases could not be ruled out.

A representative case that was not coded as an overdose, but was confounded by fever is described below:

This case involved a 4 year old girl who had a seizure 30 minutes after ingesting one Children's Benadryl Allergy fastmelt (12.5 mg of diphenhydramine HCl) for the treatment of nausea. This dose exceeded the recommended dosage for the 2 to 6 years of age group. During the seizure, she vomited several times and then became unconscious. No concomitant medications were reported. She was reported to have a fever of 102.8 º F. In the ER she was found to have a urinary tract infection.

Of the 7 cases, 5 cases reported the use of a single ingredient diphenhydramine product, one reported a multi-ingredient cough and cold product, and in the one remaining case it was indeterminable. Six cases reported the use of an OTC medication, none reported a prescription medication, and in the one remaining case it was unknown.

Two cases reported a death outcome, 2 cases reported a hospitalization, and of the remaining 3 cases that were medically significant, 2 reported an ER visit.

In summary, convulsions have been reported with overdoses of diphenhydramine. All 7 cases exceeded the labeled recommended dosage. Approximately 50% of the cases were confounded by concomitant antihistamines and a pre-existing medical condition; however, a temporal relationship exists with the ingestion of a diphenhydramine-containing product and subsequent convulsion(s); therefore, the contributory role of diphenhydramine could not be ruled out.

Nervous System Disorders: Depressed level of consciousness (N=27)

Twenty-seven cases reported adverse events related to depressed level of consciousness coded as *coma (7), confusional state (2), depressed level of consciousness (2), disorientation (1), lethargy (3), loss of consciousness (4), somnolence (9), and syncope (1)*.

Twenty cases reported the use of an OTC medication, none reported a prescription medication, and in the remaining 7 cases it was unknown. Of the 27 cases, 15 cases reported the use of a

single ingredient diphenhydramine product, 6 reported a multi-ingredient product, and in the remaining 6 cases it was indeterminable.

Fourteen of 27 (52%) cases involved children 2 to 5 years of age. Of 27 cases, 16 cases involved a drug overdose. The manner of overdose included an accidental drug intake by a child (7), intentional poisonings (4), and indeterminable (5). The reported events in the overdose cases included coma-7, somnolence-6, loss of consciousness-2, lethargy-1, confusional state-1, and disorientation-1. In these cases, a possible association between the use of diphenhydramine and the reported events could not be ruled out.

Of the 11 cases that were not coded as a drug overdose, 8 cases reported a dose ranging from 0.125 to 25 mg. Two of 8 cases involved children under 2 years of age and the doses did not exceed the labeled dosage for the lowest age group, per the monograph, and the remaining 6 cases reported doses that exceeded the labeled dosage for the lowest age group. The reported events were somnolence-3, loss of consciousness-2, lethargy-2, confusional state-1, and syncope-1 in these cases. Six of 11 cases were confounded by the use of concomitant medications, including other antihistamines, montelukast (neurologic events such as drowsiness and fatigue have been reported with montelukast), acetaminophen, benzocaine (lethargy and stupor have been reported with benzocaine-induced high methemoglobinemia), Elidel and pseudoephedrine (dose unspecified).

Nine cases reported a death outcome, 2 cases reported a hospitalization and of the remaining 16 cases that were medically significant, 5 reported an ER visit. All death cases were associated with a drug overdose.

In summary, depressed level of consciousness has been reported with the administration of diphenhydramine-containing products; approximately half (52%) involved children 2 to 5 years of age. The majority (81%) of cases were confounded by overdoses, or the concomitant use of more than one antihistamine-containing product or other medications; however, there were 7 cases that did not report any confounding factors. Among the 11 cases that were not coded as a drug overdose, none reported a diphenhydramine dose that was within the recommended dosage for its appropriate age group; however, 2 cases involved children under 2 years of age who received a diphenhydramine dose below the lowest labeled dose.

Cardiac Disorders (N=13)

Thirteen cases reported adverse events related to cardiac events coded as *increased heart rate (6), cardiac or cardio-respiratory arrest (5), left bundle branch block and EKG ST-T change (1), and palpitation (1).*

Of the 13 cases, 2 reported the use of a multi-ingredient cough and cold product, 7 cases reported a single ingredient diphenhydramine product, and in the remaining 4 cases it was indeterminable. Ten cases reported the use of an OTC medication, none reported a prescription medication, and in the remaining 3 cases it was unknown.

Seven of 13 cases (54%) involved children less than 2 years of age. Ten of 13 cases involved a drug overdose and reported the following cardiac events: increased heart rate (5), cardiac or cardio-respiratory arrest (4), and left bundle branch block and EKG ST-T change (1).

Six cases reported an **increased heart rate**; 3 of which reported a heart rate ranging from 110 to 192 bpm. The age ranged from 1.5 months to 4 years. Five of 6 cases involved a drug overdose, all of which involved an accidental drug intake by a child, and the adverse cardiac events were likely related to the diphenhydramine product; 1 of which reported a death outcome. The remaining case reported the administration of a single ingredient diphenhydramine product (1 mg) to a 1.5 month infant for the treatment of allergy, per the physician's recommendation, and

reported an increased heart rate following the 1st dose. The reported dose did not exceed the lowest labeled recommended dosage, per the monograph; however, there are no recommended doses for children under 2 years of age, except to consult a physician. No confounding factors were reported.

Five cases reported a **cardiac or cardiopulmonary arrest**; 4 of which involved a drug overdose and the remaining case did not report a dose. The age ranged from 3 months to 5 years. Among the 4 overdose cases, 3 involved accidental ingestions and 1 involved an intentional poisoning at daycare. One of the accidental ingestion cases reported the use of more than one antihistamine containing product (diphenhydramine and Dimetapp). The one remaining case that was not coded as an overdose provided very little information except that the cause of death was suspected to be a result of exposure to diphenhydramine.

One case reported a **left bundle branch block and EKG ST-T change** associated with an accidental ingestion of approximately 100 – 150 mg of diphenhydramine in a 1 year old infant.

One case reported **palpitations** in a 3 year old child following the ingestion of a high dose of diphenhydramine (25 mg, dose exceeds the recommended dosage for the 2 to 6 years of age group); however, this case was not coded as an overdose. The time to onset was reported as after the first dose. This case reported the concomitant use of a topical medication, Elidel (pimecrolimus, atopic dermatitis agent).

The outcomes in these 13 cases included death (4), hospitalization (4), and medically significant (3), of which one reported an ER visit.

In summary, cardiac adverse events have been reported with the administration of diphenhydramine-containing products; approximately half (54%) occurred in children less than 2 years of age. Approximately 77% of the cases involved drug overdoses. Fifteen percent of the cases were either confounded by a high dose or provided very little information; however, the contributory role of diphenhydramine could not be ruled out. Only one case reported a diphenhydramine dose that did not exceed the lowest labeled recommended dosage; however, the child was less than 2 years of age. The reported event was increased heart rate.

Respiratory Disorders (N=20)

Twenty cases reported adverse events related to respiratory disorders coded as *respiratory or cardio-respiratory arrest (7), dyspnea (4), asphyxia (2), cough (2), apnea (1), cheyne-stokes respiration (1), hypoxia (1), increased upper airway secretion (1), infantile apneic attack (1), nasal congestion (1), productive cough (1), pulmonary congestion (1), respiratory rate increased (1), sneezing (1), and yawning (1).*

Of the 20 cases, 2 reported the use of a multi-ingredient cough and cold product, 13 cases reported a single ingredient diphenhydramine product, and in the remaining 5 cases it was indeterminable. Fourteen cases reported the use of an OTC medication, none reported a prescription medication, and in the remaining 6 cases it was unknown.

Twelve of 20 cases (60%) involved children less than 2 years of age. Ten of 20 cases involved a drug overdose (an accidental drug intake by a child-6, intentional poisoning-1, an accidental overdose-1, and indeterminable-2) and reported the following adverse events: respiratory or cardio-respiratory arrest-6, dyspnea-2, asphyxia-1, apnea-1, cheyne-stokes respiration-1, hypoxia-1, infantile apneic attack-1, and pulmonary congestion-1.

Seven cases were coded as **respiratory or cardio-respiratory arrest**; one of which was also coded as **hypoxia**. The age ranged from 2 months to 5 years. Six of 7 cases involved a drug overdose (an accidental drug intake by a child-3, intentional poisoning-1, accidental overdose-1,

and indeterminable-1); and the one remaining case did not report a dose (very little information was provided in this case). Six of 7 cases reported a death outcome.

Four cases were coded as **dyspnea**; one of which was also coded as **infantile apneic attack**. The age ranged from 3 weeks to 4 years. Two of 4 cases involved a drug overdose (an accidental drug intake by a child-1 and intentional poisoning-1), and the remaining 2 cases were confounded by concomitant medications.

One case was coded as an **increased respiratory rate** and **nasal congestion** in a one month old infant who was administered 1 mg of diphenhydramine for allergies as recommended by a physician. There are no dosing recommendations for children below 2 years of age; however, the dose does not exceed the lowest labeled dose. The contributory role of diphenhydramine could not be ruled out in this case.

Two cases reported **asphyxia**; one of which was also coded as **cheyne-stokes respiration**. The ages were 3 months and 2 years. One case involved a drug overdose; an accidental drug intake by a child. In the 2nd case, a postmortem diphenhydramine level of 0.14 mg/L (therapeutic) was reported with compressional asphyxia as the cause of death.

Three cases reported **cough** or **productive cough**; one of which was also coded as **increased upper airway secretion**. Two cases were confounded, one reported a cough prior to ingesting diphenhydramine and the 2nd case was likely associated with a seizure that was also reported as an adverse event. The remaining case did not report any confounding factors but reported a diphenhydramine dose (18.75 mg) that exceeded the recommended dosage for a 4 year old.

In the remaining 4 cases, the 1st case reported **apnea** and **pulmonary congestion** and involved a drug overdose; the 2nd case reported **yawning** and was confounded by a concomitant medication; and the 4th case reported **sneezing** and involved a diphenhydramine dose that exceeded the recommended dosage for its age group, but was recommended by a physician.

In the above 20 cases, 9 cases reported a death outcome, 3 cases reported hospitalization and of the remaining 8 cases that were medically significant, 3 reported an ER visit.

In summary, respiratory adverse events have been reported with the administration of diphenhydramine-containing products, especially in children less than 2 years of age. The majority of cases (95%) were confounded by overdoses, hypersensitivity reactions, concomitant medications, or a seizure that was also reported as an adverse event; however, there was one case of an increased respiration rate that did not report any confounders and involved a dose below the lowest recommended age group.

3.2.4 Dextromethorphan

An AERS search for reports of pediatric serious adverse events associated with dextromethorphan from the past five years (1/1/2002 – 5/11/2007) retrieved 105 unique domestic spontaneous cases. The reported adverse events in the cases were categorized according to the AERS system organ class (SOC) as listed below *(a report may contain more than one adverse event term)*:

System Organ Class	Preferred Terms (*n*)
Cardiac disorders (8)	cardiac arrest (1), cardiac disorder (3), heart rate increased (2), tachycardia (1), supraventricular tachycardia (1)
Congenital, familial and genetic disorders (2)	arteriovenous malformation (2)
Eye disorders (1)	blepharospasm (1)
Endocrine disorders (1)	diabetes insipidus (1)

System Organ Class	Preferred Terms (*n*)
Eye disorders (8)	erythema of eyelid (1), eye disorder (1), eye rolling (1), mydriasis (4), vitreous disorder (1)
Gastrointestinal disorders (13)	constipation (2), diarrhoea (1), nausea (1), vomiting (9)
General disorders and administration site conditions (29)	abasia (1), condition aggravated (2), death (3), decreased activity (1), drug ineffective (1), feeling abnormal (1), gait disturbance (1), hyperhidrosis (1), hypothermia (1), irritability (2), listless (1), malaise (1), no reaction noted (1), oedema (1), pharmaceutical product complaint (5), pyrexia (2), sluggishness (1), sudden infant death syndrome (1), therapeutic response unexpected (1), unevaluable event (1)
Hepatobiliary disorders (3)	liver disorder (1), hepatic steatosis (1), hepatotoxicity (1)
Immune system disorder (13)	anaphylactic shock (2), angioedema (1), drug hypersensitivity (2), face oedema (1), hypersensitivity (3), reaction to drug excipients (1), Stevens-Johnson syndrome (1), urticaria (2)
Infections and infestations (8)	bronchitis (1), ear infection (1), nasopharyngitis (1), pharyngitis (1), pneumonia (3), upper respiratory tract infection (1)
Injury, poisoning and procedural complications (48)	accidental drug intake by child (11), accidental exposure (2), accidental overdose (2), drug dispensing error (1), drug toxicity (11), fall (1), incorrect dose administered (2), medication error (7), multiple drug overdose (3), overdose (7), wrong drug administered (1)
Investigations (11)	bacteria urine identified (1), body temperature increased (1), drug level (1), drug level above therapeutic (1), drug level increased (1), electrocardiogram abnormal (1), false positive laboratory result (1), radioallergosorbent test positive (1), toxicologic test abnormal (2), white blood cell count increased (1)
Metabolism and nutrition disorders (6)	anorexia (2), dehydration (1), hyperglycemia (1), oral intake reduced (1), oxygen saturation decreased (1)
Musculoskeletal and connective tissue disorders (5)	muscle rigidity (2), muscle twitching (2), tibia fracture (1)
Nervous system disorders (80)	*Seizure related (23)*: convulsion (18), febrile convulsion (4), petit mal epilepsy (1)
	All others (57): anoxic encephalopathy (3), brain stem haemorrhage (1), cerebral ischaemia (1), cerebrovascular accident (1), coma (4), coordination abnormal (1), depressed level of consciousness (2), dizziness (1), dyskinesia (1), encephalopathy (1), headache (1), hydrocephalus (2), hyperaesthesia (1), insomnia (4), intraventricular haemorrhage (1), lethargy (8), loss of consciousness (4), poor quality sleep (1), psychomotor hyperactivity (4), restlessness (2), somnolence (7), speech disorder (1), subarachnoid haemorrhage (1), tremor (3), unresponsive to stimuli (1)
Psychiatric disorders (20)	abnormal behaviour (2), agitation (2), apathy (1), crying (4), emotional distress (1), fear (1), hallucination (2), hallucination visual (2), logorrhea (1), nervousness (1), screaming (2), sleep disorder (1)
Renal and urinary disorders (3)	anuria (1), renal failure (1), urinary incontinence (1)

System Organ Class	Preferred Terms (*n*)
Respiratory, thoracic, and mediastinal disorders (21)	cough (2), cyanosis (2), dyspnoea (3), hyperventilation (1), lung disorder (2), pulmonary congestion (1), pulmonary oedema (1), respiration abnormal (1), respiratory arrest (2), respiratory depth increased (1), respiratory disorder (1), respiratory distress (1), respiratory failure (1), throat tightness (1), wheezing (1)
Skin and subcutaneous tissue disorders (6)	pallor (1), petechiae (1), pruritus (1), rash (1), skin discolouration (1), swelling face (1)
Social circumstances (3)	homicide (1), treatment noncompliance (1), victim of homicide (1)
Surgical and medical procedures (2)	hospitalization (1), oxygen supplementation (1)
Vascular disorders (2)	hypertension (1), hypotension (1)

A chart summary of the demographics and characteristics of the 105 dextromethorphan cases is provided in Appendix IV, and summarized below.

Males represented a higher percentage (53%) than females (41%). The age range was 1 month – 5 years, with a median of 18 months. Fifty-four percent (57) of the reports occurred in children less than 2 years of age. In children less than 2 years of age, deaths and adverse events related to drug overdoses (excluding accidental exposures), cardiac disorders, and respiratory disorders were more commonly reported. In children 2 to 5 years of age, adverse events related to accidental exposures, and convulsions were more commonly reported; depressed level of consciousness was equally represented. Among the cases with a reported indication, the majority were for treatment of cough, followed by cold.

The dose and time to onset were not well documented fields in the MedWatch reports. Based on the drug name and the milliliters reported, the dextromethorphan dose was determined in a little over half of the cases (61). Each dextromethorphan dose ranged from 0.3 – 50 mg, with a median of 5 mg. The time to onset was available for 55 of the reports, with 40 (73%) cases reporting an onset of less than 1 day; 30 (55%) of which reported an onset after the first dose. Sixteen cases reported a dextromethorphan blood level ranging from 9 mcg/L – 1200 mcg/L, with a median of 140 mcg/L; 7 of which were supratherapeutic and the remaining 9 cases were within therapeutic range. One case that reported a blood level of "< 50 mcg/L" was excluded because an exact number was not provided. Dextromethorphan therapeutic blood concentrations range from 2.4 - 207 mcg/L.[30] There are limitations to accurately interpreting postmortem levels of dextromethorphan, especially considering its potential for redistribution following death; therefore, the reported drug levels cannot be used as definitive data in attempting to predict antemortem concentrations, but rather as support for known clinical findings.[31,32]

Of the 105 cases, 78% (82) were associated with the use of an OTC product containing dextromethorphan and 16% (17) were associated with a prescription product; in the remaining 6 cases it was unspecified. The trade name of the primary cough and cold product was reported in

[30] Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of Over-the-Counter Cough and Cold Medications. Pediatrics. Sept 2001;108;3

[31] Leikin JB, Jerrold B, Watson WA, William A. Post-mortem toxicology: What the dead can and cannot tell us. J of Toxicology. 2003;41(1): 47-56.

[32] Cook DS, Braithwaite RA, Hale KA. Estimating antemortem drug concentrations from postmortem blood samples: the influence of postmortem redistribution. J Clin Pathol, 2000;53(4):282-5.

93 of 105 cases. Of the 105 cases, 7% (7) involved a single ingredient dextromethorphan product (Delsym-3, PediaCare Infant's Long Acting Cough-3, and Benylin DM-1) and 83% (87) involved a multi-ingredient product; in the remaining 11 cases it was indeterminable. The most commonly reported dextromethorphan containing product was PediaCare Infant's Decongestant and Cough drops (contains dextromethorphan and pseudoephedrine). Forty-six cases reported the use of concomitant medications; 17 of which reported the concomitant use of more than one cough and cold medications and 42 cases reported the concomitant use of other medications excluding cough and cold products. Cases may have reported more than one concomitant medication. Two of 17 cases reported the concomitant use of more than one dextromethorphan containing product.

Approximately 25% (28) of the cases reported a death outcome. Among the 77 cases that did not result in death, 2 reported a life-threatening event, 22 reported a hospitalization, and the remaining 53 cases reported "other."

The event date was not well documented; therefore, the received date was used to evaluate the trend. Based on the date of the reports received by the Agency from 2002 to 2007, there seemed to be an increasing trend in the number of serious adverse event reports in children less than six years of age associated with dextromethorphan. The eight reports for 2007 are not representative of the total number of reports for the year 2007 since the data was collected mid-year. A majority of the cases were reported by consumers (74%) and were submitted as expedited 15-day reports (88%).

Overdoses, nervous system disorders, cardiac disorders, and respiratory disorders are discussed in more detail below. Cases may be included in more than one category.

Deaths (N=28)[33]

Twenty-eight cases reported death as an outcome. Approximately 80% (23) of the cases involved children less than 2 years of age. Nineteen of 28 cases (68%) involved a drug overdose (intentional poisoning-5, accidental exposure-2, medication error-2, and indeterminable-10). Eighteen of 28 cases reported the use of concomitant medications; 2 of which involved the use of more than one cough and cold product containing dextromethorphan. Of the 28 cases, 16 reported the use of a multi-ingredient cough and cold product, one reported a single ingredient dextromethorphan product, and in the remaining 11 cases it was indeterminable. Fifteen of 28 cases reported the use of an OTC medication, 7 reported a prescription medication, and in the remaining 6 cases it was unknown.

All 5 of the intentional poisoning cases were confounded by high blood levels of other medications or reported multiple drug overdoses, the most commonly reported were pseudoephedrine and chlorpheniramine; in addition, one of the cases reported an overdose of medications not related to cough and cold products, to include Seroquel, valproic acid and clonidine. Despite the confounders, 3 of 5 cases reported supratherapeutic dextromethorphan blood levels (370, 380, and 390 mcg/L). The causes of death were reported as multiple drug overdose-1, pseudoephedrine toxicity-1, overdose-1, and unknown-2.

Twelve of the remaining 14 drug overdose cases reported high postmortem pseudoephedrine levels. Despite the high pseudoephedrine levels, the contributory role of dextromethorphan in these cases could not be ruled out. The cause of death was reported as follows: multiple drug

[33] Deaths are discussed for dextromethorphan, and not the other three medications (pseudoephedrine, chlorpheniramine and diphenhydramine), because the fatality data for the other three medications were previously discussed in a DDRE review: Akhavan-Toyserkani G. Safety Review: Infant mortality associated with the use of cough and cold medications. DDRE/OSE/FDA. February 6, 2007.

overdose-3, anoxic encephalopathy with drug overdose a contributing cause-2, complications of minor respiratory infection and medicinal use-1, pneumonia-1, SIDS-2, and unknown-5.

Nine cases were not coded as a drug overdose. Two of nine cases were confounded by a pre-existing medical condition, arteriovenous malformation. The 3rd, 4th and 5th cases reported dextromethorphan levels, however, none were supratherapeutic (<0.05, 40 and 59 mcg/L). One of the 3 cases reported anoxic encephalopathy and the remaining 2 cases did not report a specific adverse event other than death; the cause of death was undetermined in all 3 cases. The 6th case reported a product quality complaint and involved an 18 month old child who received one dose of concentrated Infants' Tylenol Cold Plus containing dextromethorphan, acetaminophen, and pseudoephedrine for a fever as recommended by a pharmacist and reported a seizure, hives, and limpness, 5 minutes after ingestion. The report denied a history of seizures and the child had taken the exact same product in the past without incident. The examination of the product did not reveal any evidence of product tampering or quality problems. A field sample analysis indicated the presence of acetaminophen, dextromethorphan, and pseudoephedrine. No other information was provided. The 7th and 8th cases did not report a cause of death or a specific adverse event, but the deaths occurred after the ingestion of the first or second dose of a cough and cold product; indication was reported in one case as treatment for the flu. No dosing information was provided. The 9th case implicated a single ingredient dextromethorphan product, Delsym, which involved a 4 month old infant who had chronic exposure to the drug and resulted in death. Specific adverse event, dose, indication, or medical history was not reported; however, it was speculated that the child may have been a slow metabolizer of dextromethorphan polistirex (Delsym). The cause of death was reported in one case as arteriovenous malformation and intraventricular hemorrhage, and the remaining cases did not report a cause of death.

In summary, deaths have been reported in association with the administration of cough and cold medications containing dextromethorphan, especially in children less than 2 years of age. One death case implicated a single ingredient dextromethorphan product, and although this case provided very little information and no specific adverse events were reported other than death; based on the temporal association, the role of dextromethorphan could not be ruled out. The majority (75 %) of the deaths associated with dextromethorphan were associated with overdoses, high levels of postmortem pseudoephedrine levels, multiple drug overdoses, and pre-existing medical conditions. Despite these confounders, a temporal relationship exists between the ingestion of the cough and cold products and subsequent death; therefore, the contributory role of dextromethorphan could not be ruled out.

Drug Overdose (N=41)[34]

Forty-one cases reported adverse event terms related to a drug overdose. The manner of overdose was as follows: accidental drug intake by a child (16), medication errors (11), intentional poisoning by a caregiver (5), and indeterminable (9). Of the 11 medication error cases, the types of errors were confusion between the units of measurement (4), confusion between similar sounding drug names (3), improper selection of a cough and cold product (2), caregiver misunderstanding of the dose prescribed by the physician (1), and improper re-dosing after a dose

[34] The preferred terms (PT) for these cases were coded as accidental drug intake by child, accidental exposure, accidental overdose, drug dispensing error, drug level above therapeutic, drug toxicity, incorrect dose administered, medication error, multiple drug overdose, overdose, pharmaceutical product complaint, toxicologic test abnormal, and wrong drug administered.

was spit-up (1). The DMETs review discusses 5 of the cases in further detail (ISRs: 4908951, 4921552, 4755459, 5122319, and 4633819). [35]

Twenty-four of 41 cases (59%) involved children less than 2 years of age. Twenty of 41 cases reported the use of concomitant medications; 4 of which involved the use of more than one cough and cold product containing dextromethorphan. Of the 41 cases, 40 reported the use of a multi-ingredient cough and cold product and the one remaining case reported the use of a single ingredient dextromethorphan product. Twenty-seven cases reported the use of an OTC medication, 8 reported a prescription medication, and in the remaining 6 cases it was unknown.

Twenty-two cases reported adverse events related to the nervous system, and included somnolence-5, lethargy-4, anoxic encephalopathy-3, coma-3, convulsion-3, psychomotor hyperactivity-2, loss of consciousness-2, coordination abnormal-1, decreased activity-1, hyperaesthesia-1, hypersomnia-, insomnia-1, and restlessness-1. Cases may have reported more than one neurologic adverse event. Five cases reported cardiac related adverse events, and included cardiac or cardio-respiratory arrest-2, irregular EKG-1, tachycardia-1, and an unspecified cardiac disorder-1. Nine cases reported a respiratory related adverse event, and included respiratory or cardio-respiratory arrest-3, an unspecified lung disorder-2, dyspnea-1, pulmonary congestion-1, pulmonary edema-1, and respiratory failure-1.

Nineteen cases reported a death outcome, 4 cases reported a hospitalization and of the remaining 18 cases that were medically significant, 6 reported an ER visit. The causes of death were reported as multiple drug overdose (8), anoxic encephalopathy with drug toxicity as a contributing cause (2), drug toxicity with pseudoephedrine as the predominant drug (2), complications of minor respiratory infection and medicinal use (1), SIDS (2), pneumonia (1), and unknown (3).

In summary, deaths and serious adverse events related to the nervous, cardiac, and respiratory systems have been reported with overdoses of diphenhydramine-containing products, especially in children less than 2 years of age. Among the drug overdose cases, the two largest percentages with respect to the manner of overdose were an accidental drug intake by a child (39%) and medication error (27%).

Nervous System Disorders: Convulsion (N=22)

Twenty-two cases reported adverse event terms related to seizures coded as *convulsion (17), febrile convulsion (4), and petit mal epilepsy (1)*.

Of the 22 cases, 21 reported the use of a multi-ingredient cough and cold product and the one remaining case reported a single ingredient dextromethorphan product. Nineteen cases reported the use of an OTC medication and 2 reported a prescription medication.

Fourteen of 22 cases (64%) involved children 2 to 5 years of age. Three of 22 cases involved a drug overdose. The manner of overdose was as follows: medication error-2 and indeterminable-1.

Two cases reported a convulsion that was unlikely related to the dextromethorphan containing cough and cold product based on an unlikely time course of event (time to onset was approximately 5 months), and recoding of the adverse event term to “seizure-like activity”.

Ten other cases were confounded by a history of seizures-1, concomitant medications-3, use of more than one cough and cold product containing dextromethorphan-1, diagnosis of pneumonia-

[35] DMETS review of medication errors involving OTC cough and cold medications in pediatrics. In progress as of Sept 2007.

1, suspected febrile convulsion or fever-2, suspected allergic reaction to a dye-1, and suspected tampered product-1; however, the contributory role of the dextromethorphan in these cases could not be ruled out.

Of the remaining 10 cases, one case was confounded by a possible overdose of a dextromethorphan-containing cough and cold product. A 2nd case reported a negative rechallenge. Of the remaining 8 cases, one case did not report a history of seizures. Two cases denied a fever at the time of the convulsion. The majority (6) of the cases reported a time to onset after the 1st dose. Four cases involved children 2 – 5 years of age, 3 of which reported a dextromethorphan dose that did not exceed the labeled dosage for the lowest age group, per the monograph; and one case reported a dose that was slightly above. The other 4 cases involved children less than 2 years of age, two of which reported a dextromethorphan dose that did not exceed the labeled dosage for the lowest age group, and the remaining 2 cases did not report a dose. No relevant concomitant medications were reported, other than those found in the multi-ingredient cough and cold products. Two representative cases are described below.

- A 4 year old girl who was administered Robitussin CF (10mg of dextromethorphan, dose is slightly above the recommended dosage) for a cough and had a seizure several hours after the ingestion of the 1st dose. She was post-ictal for 15 minutes following the seizure and was observed overnight in a hospital, but appeared to be in her usual state of health that evening. The mother reported the child was previously healthy with no history of seizures, and did not report a fever at the time of the seizure.
- A 21 month old infant who was administered an unknown dose of Triaminic Triaminicol Cold & Cough as recommended by a physician and reported 5 seizures within 24 hours. The onset of the first seizure occurred within 30 minutes of ingestion, and the seizures were not associated with a fever. The infant was admitted to the hospital for 2 days "for tests", and an MRI and EEG were both reported to be normal. The infant was not placed on any medications and no further seizure activity was reported.

Among the 22 cases, two cases reported a death outcome, 12 cases reported a hospitalization and of the remaining 8 cases that were medically significant, 3 reported an ER visit.

In summary, convulsions have been reported in association with the administration of cough and cold medicines containing dextromethorphan, especially in children 2 to 5 years of age. Eight cases did not report any confounding factors; 5 of which involved doses that did not exceed the labeled dosage for the lowest age group.

Nervous System Disorders: Depressed level of consciousness (N=24)

Twenty-four cases reported adverse events related to depressed level of consciousness coded as *anoxic encephalopathy (3), coma (3), depressed level of consciousness (2), encephalopathy (1), lethargy (7), loss of consciousness (4), and somnolence (8).*

Twenty cases reported the use of an OTC medication, 2 reported a prescription medication, and in the remaining 2 cases it was unknown. Of the 24 cases, 23 reported the use of a multi-ingredient cough and cold product and the one remaining case reported a single ingredient dextromethorphan product. Twelve of 24 cases (50%) involved children 2 to 5 years of age.

Fifteen of 24 cases involved a drug overdose. The manner of overdose included an accidental drug intake by child (8), intentional poisoning (2), and indeterminable (5). The reported events in the overdose cases included somnolence-6, lethargy-4, anoxic encephalopathy-3, coma-3, and loss of consciousness-2. Eight of 15 cases reported multiple drug toxicity. In these cases, a possible association between the use of dextromethorphan and the reported events could not be ruled out.

Nine cases were not coded as an overdose. The reported events in the 9 cases were lethargy-4, loss of consciousness-2, depressed level of consciousness-2, somnolence-2, and encephalopathy-1 in these cases. The time to onset was reported in 7 cases, ranging from one dose to 15 days with a median of one dose. Two of 9 cases reported relevant concomitant medications (antibiotic and metoclopramide). Eight of 9 cases reported a dose; 5 involved children 2 to 5 years of age and 3 involved children less than 2 years of age. Of the 5 cases that involved children 2 to 5 years of age, 4 cases did not exceed the labeled dose for the lowest age group, and the 5th case reported a dose (10 mg) slightly above the labeled dose for the lowest age group. Two of these 5 cases were confounded; one case reported an arteriovenous malformation and the other case reported a loss of consciousness (post-ictal) following a seizure that was also reported as an adverse event. Among the 3 cases that reported a dose in children less than 2 years of age, all 3 cases did not exceed the labeled dosage for the lowest age group.

A representative case involved a 2 year old child who was administered a dextromethorphan dose within the recommended dosage, one teaspoon of PediaCare Cough Plus Cold (dextromethorphan and pseudoephedrine; dose of dextromethorphan ingested was 7.5 mg), and following the 2nd dose reported lethargy and falling out of the crib.

Ten cases reported a death outcome, 4 cases reported a hospitalization and of the remaining 10 cases that were medically significant, 5 reported an ER visit. Of the 10 death cases, 8 cases were confounded by the use of multiple drug toxicity or high levels of medications other than dextromethorphan; the 9th case was confounded by an arteriovenous malformation where the cause of death was due to an intracranial hemorrhage, and the 10th case was reported from a literature article and involved an undetermined cause of death in a 2 month old infant born at 27 weeks of gestation. An OTC cough and cold product was suspected of playing a role in this death. The infant was hospitalized since birth for over 2 months for prematurity and discharged from the hospital eight days prior to his death. An autopsy was significant for mild acute encephalopathy with no evidence of traumatic brain injury and toxicology reports revealed what appears to be therapeutic levels of pseudoephedrine (0.23 mg/L) and dextromethorphan (<50 mcg/L).

In summary, depressed level of consciousness has been reported with the administration of cough and cold medications containing dextromethorphan. A large percentage (63%) of the cases involved overdoses. Of the 9 cases that were not coded as an overdose, 8 cases reported a dose that was within or slightly exceeded the labeled dosage for the lowest age group; 2 of which were confounded either by an arteriovenous malformation or loss of consciousness following a seizure that was also reported as an adverse event. These cases reported lethargy-3, somnolence-2, loss of consciousness-1, and depressed level of consciousness-2.

Cardiac Disorders (N=10)

Ten cases reported adverse events related to cardiac events coded as *increased heart rate (4), cardiac or cardiopulmonary arrest (2), unspecified cardiac disorder (2), irregular EKG (1), and cyanosis (1).*

Of the 10 cases, 8 reported the use of a multi-ingredient cough and cold product and in the remaining 2 cases it was indeterminable. Seven cases reported the use of an OTC medication, one reported a prescription medication, and in the remaining 2 cases it was unknown.

Eight cases (80%) involved children less than 2 years of age. Five of 10 cases involved a drug overdose and reported the following cardiac events: increased heart rate (1), cardiopulmonary arrest (1), unspecified cardiac disorder (2), and irregular EKG (1). The manner of overdose was reported as intentional poisoning (2) and medication error (3).

All 4 cases that reported an **increased heart rate** involved the concomitant use of pseudoephedrine. The age ranged from 2 months to 2 years. One case involved a drug overdose (medication error) and reported a high postmortem pseudoephedrine level but therapeutic dextromethorphan (170 mcg/mL) level. The remaining 3 cases involved dextromethorphan doses that did not exceed the labeled dose for the lowest age group, per the monograph. The time to onset was reported as one dose to 2 days. The heart rate was reported in 2 cases as 240 beats per minute (bpm) and 298 bpm. Two of 3 cases required medications (adenosine and dysopiramide-1, unspecified-1) to slow the heart rate and required hospitalization for 1 to 7 days; the 3rd patient was seen by a physician but recovered without medical treatment. One of 3 cases reported the use of a concomitant medication (acetaminophen for treatment of a fever). It was reported in one of the cases that the cardiologist suspected the cough and cold medication may have contributed to the initiation of the event. All 3 cases of increased heart rate (involving dextromethorphan doses below or within the lowest recommended dosage), were associated with the use of a multi-ingredient cough and cold product; however, the exact role of dextromethorphan could not be assessed due to the multi-ingredient nature of the products. A representative case is described below.

A representative case for increased heart rate:

- A 2 month old infant girl was administered 0.4 mL of PediaCare Infant Decongestant and Cough drops (1.25 mg of dextromethorphan) as recommended by a pharmacist for an unknown indication, and one hour after the first dose, the child cried inconsolably and would not eat. The infant was taken to the hospital where her heart rate was reported to be 240 bpm and required medications (unspecified) to slow the heart rate; she was also treated with an unspecified antibiotic. It was reported that all adverse events had resolved and the infant was released from the hospital after 7 days. No concomitant medications were reported.

Two cases reported **cardiac or cardiopulmonary arrest**. One case involved an intentional drug overdose and the other case involved a product complaint. The intentional overdose case involved a 2 month old infant who was administered a multi-ingredient cough and cold product containing dextromethorphan and pseudoephedrine and reported a high postmortem pseudoephedrine blood level but no dextromethorphan level. It also reported the concomitant use of senna. The 2nd case involved a product complaint in a previously healthy 18 month old infant who was administered 2 dropperfuls of Concentrated Infant's Tylenol Cold Plus Cough (5 mg of dextromethorphan) for the treatment of a fever as recommended by a pharmacist and 5 minutes after ingestion reported a seizure that resulted in a cardiac arrest and death (described in the deaths section). No past medical history regarding seizures was reported. However, it was reported the infant had received the exact same product in the past without incident, but no information was reported regarding the age and dose at which it was administered in the past. An examination of the product did not reveal any evidence of product tampering or quality problems. No concomitant medications were reported. An autopsy report is pending but has not been reported to date. Despite the high pseudoephedrine level and unlikely time course of events (time to onset of 5 minutes), the contributory role of dextromethorphan in these 2 cases could not be ruled out.

Two cases reported an **unspecified cardiac disorder**. Both cases involved a drug overdose. The 1st case involved an intentional drug overdose, which was confounded by several concomitant medications (valproic acid, clonidine, chlorpheniramine, and Seroquel); however, the contributory role of dextromethorphan could not be ruled out. The 2nd case involved a medication error where a 4 month old infant was prescribed one mL of Bromfed DM but the label on the bottle read 5 mL (10 mg of dextromethorphan). The infant was treated with charcoal and gastric lavage, and discharged home. The contributory role of dextromethorphan in these cases could not be ruled out.

One case reported an **irregular EKG** associated with an overdose (an accidental drug intake by a child) of a cough and cold product, however, the exact role of dextromethorphan could not be assessed due to the multi-ingredient nature of the product.

One case reported "**cyanosis around the mouth."** This case involved a 3 week old infant who was administered a pseudoephedrine/dextromethorphan combination product where the dextromethorphan dose (1.25 mg of dextromethorphan per dose) did not exceed the labeled dosage for the lowest age group; however, there are no dosing recommendations for children less than 2 years of age, per the monograph. The report stated the "child's mouth turned blue" following the ingestion of 3 to 4 doses. The indication for treatment was cough. The child was admitted to a hospital and an electrocardiogram revealed the child had "two small holes in his heart."

The outcomes in the above 10 cases were reported as follows: death (4), hospitalization (4), and of the remaining 2 cases that were medically significant, one reported an ER visit.

In summary, cardiac adverse events have been reported with the administration of cough and cold medicines containing dextromethorphan, especially in children less than 2 years of age. Four of 8 cases involved dextromethorphan doses that did not exceed the labeled dosage for the lowest age group, per the monograph; and reported the following cardiac events: increased heart rate-3, and cardiac arrest-1. The remaining 4 of 8 cases involved drug overdoses and reported the following cardiac events: cardiopulmonary arrest-1, unspecified cardiac disorders-2, and irregular EKG-1.

Respiratory Disorders (N=15)

Fifteen cases reported adverse events related to respiratory disorders coded as *respiratory arrest (3), dyspnea (2), lung disorder (2), nasal congestion (2), cough (1), hyperventilation (1), pulmonary congestion (1), pulmonary oedema (1), respiration abnormal (1), and respiratory failure (1).*

Of the 15 cases, 11 reported the use of a multi-ingredient cough and cold product, one reported a single ingredient dextromethorphan product, and in the remaining 3 cases it was indeterminable. Nine cases reported the use of an OTC medication, 4 reported a prescription medication, and in the remaining 2 cases it was unknown.

Ten of 15 cases (67%) involved children less than 2 years of age. Nine cases involved a drug overdose (intentional poisonings-2, an accidental drug intake by a child-1, medication error-1, and indeterminable-5).

Eight cases reported **respiratory arrest, respiratory failure, pulmonary edema, pulmonary congestion,** or **lung disorder**. The ages ranged from 2 months to 4 years. All 8 cases involved a drug overdose; and all were confounded by multiple drug toxicity, most commonly pseudoephedrine. Despite the confounding, 3 of 8 cases also reported a supratherapeutic dextromethorphan level; therefore, the contributory role of dextromethorphan could not be ruled out from these cases.

The remaining 7 cases that reported **dyspnea, nasal congestion, cough, hyperventilation, and respiration abnormal** were confounded by an overdose-1, likely secondary event to a seizure-1, pre-existing cold symptom-3, pre-existing medical condition (arteriovenous malformation)-1, and concomitant medication-1. Despite the confounders, the contributory role of dextromethorphan could not be ruled out in approximately half of the cases.

Among the 15 cases, 9 cases reported a death outcome, 3 cases reported a hospitalization and of the remaining 3 cases that were medically significant, 2 reported an ER visit.

In summary, 60% of the cases were associated with an overdose of a dextromethorphan-containing product. The remaining 40% (4) of the cases were confounded by concomitant

medications-1, pre-existing medical conditions or cold symptoms-3, and a secondary event to a seizure that was also reported as an adverse event-1.

4 EPIDEMIOLOGY

The Toxic Exposure Surveillance System (TESS) is a poisoning surveillance database maintained and owned by the American Association of Poison Control Centers (AAPCC) in cooperation with 61 local and regional poison control centers in the U.S. TESS represents data from a collection of poisoning-related calls to U.S. poison control centers. In 2005 (the latest year for which we have data), poison control centers linked with AAPCC served nearly 296 million of the U.S. population. From 1983 when TESS was started, to the present time, this database contains 41 million human poison exposure cases including 2.4 million cases reported in 2005 alone. [36]

4.1 METHODS

The AAPCC's annual reports of 2001, 2002, 2003, 2004 and 2005 that summarize TESS data were reviewed to determine the extent of poisoning in association with exposure to cough and cold products. Two tables in the annual reports (Table 21: Summary of Fatal exposures, and Table 22B: Demographic Profile of Exposure Cases by Generic Category of Substances and Products) were reviewed and formed the basis of this report. Two therapeutic classes/categories of drugs under Table 21 and Table 22 namely (1.) 'Antihistamines' and (2.) 'Cold and cough' preparations were specifically reviewed to identify cases of poisoning with drugs of interest. We do not know how 'cold and cough' preparations are defined by AAPCC or which ingredients are included under this category. This information is not publicly available. Only those cases that listed a 'cold and cough' preparation, or the antihistamine diphenhydramine (to be consistent with the drug list specified in the review of spontaneous case reports submitted to AERS) as the primary (first) agent were included.

Toxic exposure calls received at the poison control centers in the U.S. are managed and assessed by health care professionals who are pharmacists, nurses, or physicians with additional training in clinical toxicology. Based on their clinical expertise and judgment, these specialists in poison information use the collected information about the patient, the toxic agent and the circumstances of the exposure as a basis for advice on appropriate medical care and triage the patient to either home or health care facility. Additional follow-up calls are made to determine the outcome of the toxic exposure. In 2005, 3.9 million follow-up calls were made by poison control centers to provide additional patient guidance, confirm compliance with recommendations, and to determine the outcome of the exposure. Follow-ups were done in about 45% of human exposure cases. One or multiple follow-up calls were made in about 22% of cases. The information collected is entered electronically into a relational database which is then up-linked to the central TESS database.[36,37]

Definitions and terminology used:

In the annual reports, '*major effect'* is defined as signs or symptoms occurring as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement.

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[36] Lai MW, Klein-Schwartz W, Rodgers GC, Abrams JY, Haber DA, Bronstein AC, Wruk KM. 2005 Annual Report of the American Association of Poison Control Centers' national poisoning and exposure database. Clin Toxicol (Phila). 2006;44:803-932.

[37] Woolf AD, Watson WA, Smolinske S, Litovitz T. The severity of toxic reactions to ephedra: comparisons to other botanical products and national trends from 1993-2002. Clin Toxicol 2005;43:347-55.

'*Death*' is when a patient dies as a result of the exposure or as a direct complication of the exposure. Only those deaths that are probably or undoubtedly related to the exposure are coded in TESS.

In TESS, an *'exposure'* is defined as an actual or suspected contact with any substance that has been ingested by, inhaled by, absorbed by, applied to, or injected into the body. The various reasons for exposure are defined as it appears in the TESS annual report. '*Intentional misuse'* is an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. '*Intentional abuse'* is an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to achieve a euphoric or psychotropic effect. All recreational use of substances for any effect is included. '*Intentional unknown'* is an exposure that is determined to be intentional but the specific motive is unknown. '*Unintentional unknown'* is an exposure determined to be unintentional but the exact reason is unknown. '*Unintentional general'* includes all unintentional exposures not specifically defined. '*Adverse reaction'* is defined as 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 caused by 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 coded instead as a therapeutic error. '*Therapeutic error'* is defined as 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 substituted for medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are known to interact are also included. '*Suspected suicidal'* is defined as an exposure resulting from the inappropriate use of a substance for reasons that are suspected to be self-destructive or manipulative. '*Malicious*' is used to capture patients who are victims of another person's intent to harm them.

Acute exposure is defined as a single, repeated or continuous exposure occurring over a period of 8 hours or less. Chronic exposure is defined as a continuous, repeated or intermittent exposure to the same substance in a period exceeding 8 hours.

Acute-on-chronic is defined as a single exposure preceded by a continuous, repeated or intermittent exposure occurring over a period exceeding 8 hours.

Health care facilities include acute care hospitals, physician offices or clinics, and freestanding emergency centers. Non-health care facility refers to the site of exposure that is usually the patient's home.

4.2 RESULTS OF TOXIC EXPOSURE SURVEILLANCE SYSTEM DATABASE

Poisoning Exposures with 'cough and cold' preparations:

The frequency of reports to U.S. poison control centers involving all human exposures to agents classified by TESS as cough and cold preparations for the 5-year period (2001 to 2005) is shown in Table 5. Without stratification by age, the total number of reports increased slightly from 97,710 in 2001 to 116,084 in 2005. With restriction to the subset of reports for individuals aged < 6 years, U.S. poison control centers collected nearly 60,000 reports associated with cough and cold preparations in 2001; this increased to about 70,000 in the 2005. However, the overall percentage of children under 6 years of age among all reports in association with cough and cold preparations remained almost constant throughout this 5-year review period at around 61%-62%. For any of the years included in this analysis, the vast majority (81%-82%) of these reports ***for all***

ages were classified as *unintentional*. Additionally, for any of the years and ages included in this analysis only 22% to 24% of these reports received care at a health care facility.

Table 5. Total Reports in association with Cough and Cold preparations in TESS and the Number (%) of reports and Fatalities in Children age < 6 years, 2001-2005

Year	Total (N)	Age <6 yrs (N)(%)	Fatalities Age <6 yrs (N)
2001	97,710	59,949 (61%)	NR
2002	100,612	62,107 (62%)	3
2003	112,173	68,493 (61%)	6
2004	108,814	67,494 (62%)	2
2005	116,084	70,398 (61%)	1

Table 5 shows 14 fatalities recorded in the TESS database in 2001-2005, in association with "cough and cold" and diphenhydramine products in children under 6 years of age. These 14 fatalities (12 in association with "cough and cold" products and 2 with diphenhydramine preparations) are described in more detail in Table 6 which provides a line listing for each of the 14 cases that resulted in fatality with the name(s) of the product, the age of the child, route, and the reason of ingestion (intentionality). Most cases (8 of 14) were classified as therapeutic error (n=4) or unintentional general (n=4). The remaining cases were adverse reaction (n=2), malicious (n=2), and the reason was unknown in two cases. Three cases (Cases # 4, 7, and 11) were associated with ingestion of a single-ingredient (diphenhydramine (n=2), dextromethorphan (n=1)) preparation. In four cases (Case # 3, 5, 6, and 13), a prescription product containing chlorpheniramine and hydrocodone was involved; one of these cases (#6) included concomitant use of ibuprofen.

Table 6. Summary of Fatalities in Association with "Cough/Cold" and Diphenhydramine Preparations in TESS, 2001-2005

Case #	Year	Name (s) of Product	Age of Child	Route	Reason of Ingestion
1	2002	Brompheniramine/Pseudoephedrine	4 months	Ingestion	Therapeutic error
2	2002	Chlorpheniramine/Dextromethorphan/ Pseudoephedrine; Brompheniramine	3 years	Ingestion	Unintentional general
3	2002	Chlorpheniramine/Hydrocodone	2 years	Ingestion	Therapeutic error
4	2003	Diphenhydramine	3 months	Ingestion	Unknown
5	2003	Chlorpheniramine/Hydrocodone	3 years	Ingestion	Therapeutic error

Case #	Year	Name (s) of Product	Age of Child	Route	Reason of Ingestion
6	2003	Chlorpheniramine/Hydrocodone; Ibuprofen	3 years	Ingestion	Unintentional general
7	2003	Dextromethorphan	4 months	Ingestion	Adverse reaction
8	2003	Pseudoephedrine;Acetaminophen/ Pseudoephedrine	3 months	Ingestion	Therapeutic error
9	2003	Pseudoephedrine; Amoxicillin	4 months	Aspiration/ Ingestion	Malicious
10	2003	Pseudoephedrine; Diphenhydramine; Phenylpropanolamine	2 years	Ingestion	Unintentional general
11	2004	Diphenhydramine	5 years	Ingestion	Malicious
12	2004	Chlorpheniramine/Guaifenesin/ Phenylephrine	4 months	Ingestion	Adverse reaction
13	2004	Chlorpheniramine/Hydrocodone	12 months	Ingestion	Unintentional general
14	2005	Pseudoephedrine/Dextromethorphan; Senna	2 months	Unknown	Unknown

Poisoning Exposure with Diphenhydramine Preparations:

Tables 7 summarizes the poisoning exposure cases of all diphenhydramine preparations including when OTC/Rx status was unknown. There are a substantial number of reports of poisoning exposures with diphenhydramine preparations overall and there has been a slight increase in the number of cases from 28,263 in 2001 to 31,282 in 2005. Almost half of these cases (over 12,000 per year) involved children under 6 years of age. However, the overall percentage of cases <6 years of age has remained constant over the 5-year review from 43-46%. During the review period, the reason for ingestion was accidental or unintentional in a significant percentage (45-75%) of the cases for all ages and on an average 42% of the cases required treatment in a health care facility.

Table 7. Exposures to Diphenhydramine Preparations in TESS

Year	Total	<6 yrs (%)	Fatalities (Age <6 years)
2001	28,263	13,044 (46%)	0
2002	28,133	12,558 (45%)	0
2003	28,092	12,089 (44%)	1
2004	29,501	12,468 (42%)	1
2005	31,282	13,445 (43%)	0

5 DISCUSSION

There are limitations of quantitatively analyzing a spontaneous reporting database such as AERS. One limitation is that an adverse event report may contain concomitant use of other medications and/or multiple ingredient products, and therefore, a clear drug-event association is often difficult to establish. The decongestants, antihistamines, and antitussives discussed in this consult are found in many OTC preparations either as single-ingredient preparations, or more commonly in combination of at least two or more ingredients. Other limitations include underreporting due in part to the length of time these products have been on the market. Under 21 CFR 341 there were no reporting requirements for OTC monograph products for the time period searched in AERS, which makes it especially difficult to obtain a true number of adverse events (numerator) for these products. There are legislative changes that will be effective December 22, 2007 requiring manufacturers of dietary supplements and over-the-counter monograph products to submit serious adverse event reports to the FDA. In addition, interpretation of spontaneous reported events is difficult in the absence of a control group.

However, the AERS cases demonstrate that the administration of cough and cold medicines in children less than 6 years of age could lead to serious adverse events including death. The key findings are as follows:

- The number of unique domestic cases of serious adverse events associated with each drug is as follows: pseudoephedrine 150, chlorpheniramine 63, diphenhydramine 83, and dextromethorphan 105.
- Approximately 30% of the serious adverse event cases associated with pseudoephedrine, chlorpheniramine, diphenhydramine, or dextromethorphan reported a death outcome.
- Over 50% of the reported serious adverse events associated with pseudoephedrine and dextromethorphan occurred in children less than 2 years of age.
- Over 50% of the reported serious adverse events associated with chlorpheniramine and diphenhydramine occurred in children 2 to 5 years of age.
- Both OTC and prescription products were reported cases; however, the majority of the cases were associated with the use of an OTC cough and cold product (56-78%). The use of a prescription cough and cold product was reported in 14% of the cases.
- More than 75% of the reports associated with pseudoephedrine, chlorpheniramine, and dextromethorphan involved the use of a multi-ingredient cough and cold product.
- Drug overdoses associated with pseudoephedrine, chlorpheniramine, diphenhydramine, or dextromethorphan contributed to serious adverse events in approximately 48% of the cases.
    - Approximately 22% of the cases reported an accidental exposure that resulted in a serious adverse event.
    - Approximately 6% of the cases reported an intentional overdose by a caregiver resulted in a serious adverse event.
    - Approximately 16% of the cases reported a medication error that resulted in a serious adverse event to include prescribing errors, dispensing errors, administration errors, duplication of therapy, and wrong drug administration.
    - The manner of overdose could not be determined in the remaining 56% of the cases.

- Serious adverse events and deaths related to the nervous system, cardiac system, respiratory system, and other notable events have been reported with overdoses of cough and cold medications as well as in cases where the dose did not exceed the labeled dose for the lowest age group.
    - In particular, convulsions have been reported with the administration of cough and cold medications, more commonly in children 2 years of age and older. Convulsions were more common in settings outside of an overdose.
    - Serious cardiac events (cardiac arrest, cardio-respiratory arrest, cardiac failure, tachycardia, supraventricular tachycardia) and respiratory events (respiratory distress, respiratory arrest, respiratory failure, dyspnea, apnea) have been reported following the ingestion of cough and cold medications mostly in the setting of a drug overdose. However, serious cardiac and respiratory events were reported in cases where the dosage did not exceed the labeled dose for the lowest age group.

The AERS cases demonstrate that the OTC cough and cold product are often administered to children below the lowest labeled dose. Since there are no dosing recommendations for children under the age of 2 for pseudoephedrine and dextromethorphan and under the age of 6 for the OTC antihistamines, most of these cases could be considered off-labeled use. Lack of proper dosage guidelines below the recommended age may be contributing to serious adverse events, especially in children less than 2 years of age. Dosages for cough and cold products are generally age based and are provided as a range. Age based dosing may lead to increased risk of overdose, especially in infants who are below the average weight or are born premature. Among the pseudoephedrine cases, approximately 6% reported serious adverse events in infants born prematurely.

Furthermore, dosing suggestions for these products are often published by the manufacturers and are extrapolated from adult dosing. In the AERS database there were reports of serious adverse events associated with dosages that did not exceed the recommended dosage for the lowest age group as well as cases that reported a drug overdose with the manner of overdose as undetermined. This raises the concern of whether dose extrapolation is appropriate for the cough and cold products in children less than 2 years of age for pseudoephedrine and dextromethorphan and less than 6 years of age for the chlorpheniramine and diphenhydramine.

Approximately 16% of the cases reported a medication error associated with a cough and cold medication that resulted in a serious adverse event. These errors resulted from prescribing errors, dispensing errors, administration errors, duplication of therapy, and wrong drug administration. Parents and prescribers may be misinformed that OTC cough and cold medications intended for children 2 years and above are also safe in younger children and infants. Parents and caregivers may not be aware of the duplication of ingredients and the potential risk of overdose when using multiple products. Most cough and cold preparations are combinations of at least 2 or more ingredients, and it is unclear as to which active ingredient the dose is based on. Furthermore, there is also the potential for confusion between the children's cough/cold products and the infants' concentrated drops (higher concentration) in regards to the dosing regimen that could lead to adverse events.

Each year, an estimated 4 million poisoning episodes have been reported in the U.S. with approximately 300,000 cases resulting in hospitalization.[38] As reported here, in the last five years (2001-2005), on an average each year there have been over 100,000 calls recorded in TESS, the

[38] Committee on Poison Prevention and Control. Forging a Poison Prevention and Control System. National Academy of Sciences. Washington, DC. 2004

database of the U.S. poison control centers, related to poisoning/overdose exposures with 'cough and cold', and diphenhydramine preparations. While the total number of calls have increased slightly over the years, the percentage of calls involving children less than six years has remained constant and constitutes about 40-60% of all calls. From the DSRCS review (Governale L. Over-the-counter and prescription use of cough/cold products. August 9, 2007) for cough/cold products, it appears that dispensation of prescription cough/cold preparations in the age group 0-6 years accounted for approximately 3.9 million prescriptions or 12% of the entire cough/cold market in 2006. We do not have reliable demographic data for OTC cough and cold products usage. However, from the TESS data it appears that children less than 6 years of age were the subject of about 40-60% of all calls related to cough and cold' and diphenhydramine preparations.

We do not know the extent of underreporting to poison control centers but it has been reported that there is substantial underreporting of fatal poisoning cases to poisoning control centers. The authors state that the reporting rates of poisoning exposures may be even poorer in sites further away from a regional poison center. [39] In one study it was found that among 533 cases of poisoning/drug overdoses reported to an emergency department, less than 1 in 4 were reported to the regional poison control center in the catchment area.[40] In another study, poisoning related deaths reported to the state medical examiner were compared with those reported to the regional poison center. During this study period, 389 poisoning related deaths were reported to the medical examiner compared to 45 deaths recorded by the poison center.[41] Recently in 2005, an investigation by the Centers for Disease Control and Prevention (CDC) and the National Association of Medical Examiners (NAME) identified three deaths in infant's aged < 6 months in association with cough and cold medications.[42] However, this review of TESS data identified only one death in 2005 in an infant of 2 months old related to cough and cold medication and thereby supporting the hypothesis that fatal poisoning cases are not always reported to poison control centers. On further review the solo case identified in TESS was found to be different from the three cases identified by CDC/NAME investigators. Only a minority of deaths attributed to poisoning are reported to poison control centers and hence the true number of deaths associated with 'cough and cold' and diphenhydramine preparations in children could be substantial.

In addition to identification of reports linked to 'cough and cold' and diphenhydramine preparations, this review also included 4 fatalities (of 14 in total) in association with the combination product containing the antihistamine chlorpheniramine and the opioid hydrocodone. It is beyond the scope of this review to suggest that there is an interaction between hydrocodone and chlorpheniramine.

Therefore, as recorded in the TESS database, overdose and poisoning-related therapeutic misadventures in association with 'cough and cold' and diphenhydramine preparations accounted for about 110,000 calls in 2001 and increased to 147,000 calls in 2005. Approximately 40-60% of

[39] Blanc PD, Kearney TE, Olson KR. Underreporting of fatal cases to a regional poison control center. West J Med 1995;162:505-509

[40] Blanc PD, Jones MR, Olson KR. Surveillance of poisoning and drug overdose through hospital discharge coding, poison control center reporting, and the Drug Abuse Warning Network. Am J Emerg Med 1993;11:14-9

[41] Linakis JG, Frederick KA. Poisoning deaths not reported to the regional poison control center. Ann Emerg Med. 1993;22:1822-8

[42] Anonymous. Infant deaths associated with cough and cold medications – two states, 2005. MMWR 2007;56:1-4

these calls involve children < 6 years of age. In the last 5 years, there were a total of 14 deaths attributed to 'cough and cold' and diphenhydramine preparations in children < 6 years of age recorded in the TESS database. The majority of these cases were associated with unintentional poisoning. Both OTC and prescription products have been involved in these poisoning/overdose cases. Notably, 4 of the 14 deaths were associated with the ingestion of a combination product containing chlorpheniramine and hydrocodone. Because of the problem of underreporting of poisoning/overdose cases, the true number of cases may be considerably higher.

6 CONCLUSION/RECOMMENDATIONS

In conclusion, both the AERS and TESS data suggest that the use of prescription and OTC cough and cold medication in children younger than 6 years of age have been associated with serious adverse events, including death. It is important to put these risks in the context of any potential benefits of these products which, in children under 6 years of age, have largely not been quantified (Ref Cough and Cold Monograph). Therefore, we recommend an educational campaign directed towards healthcare providers and parents/caregivers that addresses proper education about cough and cold products; in particular, the risks of using these products in children less than the minimum age recommended in the monograph, as well as the potential risk of overdose when using multiple cough and cold products. With the known lack of evidence of efficacy in children and in view of the current safety data on the potential for drug toxicity, the labeling of cough and cold products (both prescription and OTC) should include prominent language to describe the risk of overdose in children. Also, the statement "consult a physician" for decongestants and antitussives in patients under 2 years of age and in patients under 6 years of age for antihistamines should be reconsidered. In the absence of specific dosing instructions, we suggest that the revised wording state that dosing is not recommended in these age groups. Further, a timely forum among stakeholders is recommended to discuss making only single ingredient cough and cold products available for pediatric formulations.

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APPENDICES

Appendix I. Summary of Demographics and Characteristics of AERS Pseudoephedrine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=150)		
Sex		
	Male	86
	Female	54
	Unknown	10
Age (n=147)		
	0 – 2 months	18
	3 – 11 months	39
	12 – 23 months	25
	2 years	32
	3-5 years	33
	Median = 18 months	
	Range = 2 weeks – 5 years	
Indication		
	Allergy – 3	Congestion – 9
	Ear &Sinus infection – 3	Cough – 15
	Cold – 21	Fever – 6
	Nasopharyngitis – 8	Flu – 3
	Teething – 2	URI – 6
	Rhinorrhea – 4	Accidental exposure – 20
	hypersensitivity– 1	Unknown - 49
Each Dose		
	2.25 mg – 1	15 mg – 24
	3 mg – 1	22.5 mg – 1
	3.75 mg - 15	24 mg - 1
	6 mg – 1	37.5 mg - 1
	7.5 mg – 6	47 mg – 2
	11.25 – 3	> 50 mg - 4
	12.5 – 1	Unknown – 89
Time to onset		
	1 dose - 52	5 days – 2
	2 doses – 5	6 days – 1
	3 doses - 1	7 days – 2
	1 day – 14	10 days – 1

Appendix I. Summary of Demographics and Characteristics of AERS Pseudoephedrine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=150)		
	2 days – 9	≥ 2 weeks – 1
	3 days – 1	Unknown – 61
Drug Levels[¥] (N=33)		
	< 1 mg/L	10
	1 – 10 mg/L	17
	> 10 mg/L	6
Product Classification[†]		
	OTC	106
	Rx	19
	Unknown	25
Product Type[†]		
	Single ingredient	15
	Combination/multiple ingredient	113
	Unknown	22
Reported Drug Name[‡]		
	Accuhist Pediatric – 2	PediaCare Children's Nightrest Cough and Cold Liquid – 6
	acetaminophen/pseudoephedrine – 2	PediaCare Cough Plus Cold Chewable – 2
	Benadryl Allergy/Sinus – 5	PediaCare Children's Cough/Cold Liquid – 2
	Benadryl Children's Allergy and Sinus – 3	PediaCare Decongestant (unspecified) – 1
	Benadryl Children's Allergy and Cold – 1	PediaCare Infant's Decongestant – 7
	Bromfed DM – 1	PediaCare Infant's Decongestant and Cough – 26
	Carbaxefed DM RF – 4	PediaCare Infant's Long Acting Cough Liquid – 1
	Cardec DM – 2	Pseudoephedrine – 22
	Cardec DM drops – 1	Robitussin Pediatric Night Relief – 1
	Children's Advil Cold – 3	Rondec DM – 3
	Children's Motrin Cold – 4	Sudafed – 4
	Concentrated Infant's Tylenol Cold Plus – 3	Sudafed (unspecified) – 1
	Children's Tylenol Cold and Cough – 2	Sudafed Children's Nasal Decongestant – 1
	Children's Tylenol Sinus – 1	Sudafed Children's Cough and Cold Liquid – 2
	Claritin –D 24 hour – 1	Sudafed Sinus and Cold – 1
	Dextromethorphan/pseudoephedrine –	Tanafed DMX suspension – 1

Appendix I. Summary of Demographics and Characteristics of AERS Pseudoephedrine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=150)		
	1	
	Dimetapp – 1	Triaminic Cold and Allergy – 3
	Drixoral Cold and Allergy – 1	Triaminic Cold and Cough – 4
	Efidac – 1	Triaminic Cold and Night Time Cough – 3
	Nyquil Children's Cold/Cough Relief – 2	Triaminic Cough and Sore Throat – 2
	Panmist – 1	Tussend – 1
	PediaCare Children's Long Acting Cough Plus Cold – 5	12 Hour Pseudoephed – 1
	PediaCare Children's Multi-Symptom Cold – 8	
Concomitant Cough and Cold Medications[§] (N=16)		
	Benadryl Allergy – 1	Doxylamine – 2
	Brompheniramine – 3	Ephedrine – 4
	Bromaxafed DM – 1	Guaifenesin – 4
	Carbinoxamine – 4	Infant Tylenol Cold – 1
	Chlorpheniramine – 1	Phenylpropanolamine – 4
	Dextromethorphan – 8	Triaminic Cold & Night Time Cough – 1
	Diphenhydramine – 1	
	Dimetapp (unspecified) – 1	
Other Concomitant Medications[£] (N=46)		
	acetaminophen – 15	Lamotrigine – 1
	Albuterol – 1	Lansoprazole – 1
	amoxicillin – 4	Levorphanol – 2
	Anaprox – 1	Macrogol (laxative) – 1
	antibiotic (unspecified) – 2	Metoclopramide – 1
	benzocaine – 1	Multivitamin – 1
	Cod liver oil – 1	Oxcarbazepine – 1
	Diflucan – 1	Oxycontin – 1
	Ex-Lax – 1	phenobarbital– 1
	Flovent – 1	saline mixture – 2
	Ibuprofen – 4	Senna – 1
	Immodium – 1	Viaxin – 1
	Immunization – 1	Zyrtec – 3
Outcome		

Appendix I. Summary of Demographics and Characteristics of AERS Pseudoephedrine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=150)		
	Death	43
	Life Threatening	1
	Hospitalization	27
	Other	79
Receive Year		
	2002	8
	2003	27
	2004	24
	2005	34
	2006	40
	2007 (January to May 11)	17
Reporter Type		
	Healthcare Professional	47
	Consumer	102
	Unknown	1
Type of Report		
	15-Day	133
	Direct	14
	Periodic	3

[¥] Data compiled from previously published scientific literature and from prior Office of the Chief Medical Examiner (OCME) experience report a therapeutic pseudoephedrine level of less than 1 mg/L and lethal levels of above 10.0 mg/L

[†] Product classification was determined based on trade name or per report

[‡] The drug name is the verbatim name provided by the reporter or as specified per report. Only the primary cough and cold medication was included. Only one cough and cold product was mentioned per case.

[§] The concomitant cough and cold medications include trade names or ingredients of concomitant cough and cold medications that were reported, excluding the primary cough and cold medication listed in the reported drug name. Cases may have reported more than one concomitant cough and cold medication.

[§] The concomitant cough and cold medications include cough and cold medications that were not identified as the primary cough and cold medication in the reported drug name category. Cases may have reported more than one concomitant cough and cold medication.

[£] Other concomitant medications include all other non-cough and cold medications that were reported.

Appendix II. Summary of Demographics and Characteristics of AERS Chlorpheniramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=63)		
Sex		
	Male	40
	Female	22
	Unknown	1
Age		
	0 – 2 months	2
	3 – 11 months	6
	12 – 23 months	14
	2 years	15
	3-5 years	26
	Median = 2 years	
	Range = 1 month – 5 years	
Indication		
	Cold – 5	Post nasal drip – 1
	Cough – 7	Allergy – 1
	Congestion – 3	Reactive airway disease – 2
	Rhinorrhea – 1	Accidental ingestion – 6
	Nasopharyngitis – 2	Otitis media – 1
	URI – 3	Sleep – 1
	Fever – 2	Unknown – 28
Each Dose		
	0.05 mg – 2	3 mg – 1
	0.15 mg – 1	4 mg – 4
	0.25 mg – 1	5 mg – 1
	0.5 mg – 3	6 mg – 2
	1 mg – 9	8 mg – 2
	1.25 mg – 1	12 mg – 1
	2 mg – 2	Unknown – 31
	2.25 mg – 2	
Time to onset		
	1 dose – 20	3 days – 3
	2 doses – 4	7 days – 1

Appendix II. Summary of Demographics and Characteristics of AERS Chlorpheniramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=63)		
	3 doses – 2	10 days – 2
	1 day – 1	Unknown – 27
	2 days – 3	
Drug levels[¥]		
	< 0.01 mg/L	0
	0.01 – 0.02 mg/L	0
	> 0.02 mg/L	6
Product Classification[†]		
	OTC	35
	Rx	20
	Unknown	8
Product Type[†]		
	Single ingredient	0
	Combination/multiple ingredients	55
	Unknown	8
Reported Drug Name[‡]		
	Atuss DR – 1	Rynatuss adult tablet – 1
	Chlor-Med D Liquid – 1	Tannihist 12-RF Suspension – 2
	chlorpheniramine – 8	Tetra Tannate Pediatric Suspension – 1
	chlorpheniramine/hydrocodone – 1	Triaminic 12 – 2
	Endagen HD – 1	Triaminic Cold & Allergy – 1
	generic Rynatan – 1	Triaminic Cold & Cough Liquid – 7
	Nyquil Children's Cold/Cough Relief – 1	Triaminic Cold & Night Time Cough Liquid– 3
	Pancof-PD – 1	Triaminic Expectorant Chest & Head Congestion – 1
	PediaCare Children's Multi-Symptom Cold Liquid – 5	Triaminic/Sudafed – 1
	PediaCare Children's Multi-Symptom Cold Chewables – 1	Triaminic Severe Cold and Fever – 1
	PediaCare Children's Nightrest Cough & Cold – 7	Triotann Pediatric Suspension – 1
	PediaCare Cough/Cold Chewables – 1	Tussi 12 – 1
	PediaCare Cough/Cold Liquid – 1	Tussionex ER Suspension – 8
	Polytussin DM – 1	Tylenol Children's Plus Cold & Cough – 1

Appendix II. Summary of Demographics and Characteristics of AERS Chlorpheniramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=63)		
	Robitussin Pediatric Night Relief – 1	
Concomitant Cough and Cold Medications [§] (N=13)		
	Benadryl – 1	guaifenesin – 1
	brompheniramine – 1	Phenchlor Tannate Pediatric suspension – 1
	carbinoxamine – 2	pseudoephedrine – 2
	dextromethorphan – 3	Triaminic Cold & Night Time Cough Liquid– 1
	Dimetapp (unspecified) – 1	Triaminic Triaminicol – 1
	diphenhydramine – 2	
Other Concomitant Medications [£] (N=27)		
	acetaminophen – 11	Macrogol – 1
	antibiotic (unspecified) – 2	Omnicef – 1
	albuterol – 1	oxcarbazepine – 1
	benzocaine – 1	Pulmicort respules – 1
	clonidine – 1	metoclopramide – 1
	Depakote – 1	NORCO – 2
	Doxepin – 1	phenobarbital – 2
	Ex-Lax – 1	Seroquel – 1
	ibuprofen – 6	valproic acid – 1
	Imodium – 1	Zyrtec – 1
Outcome		
	Death	20
	Life Threatening	1
	Hospitalization	16
	Other	26
Receive Year		
	2002	6
	2003	19
	2004	16
	2005	8
	2006	11
	2007 (January to May 11)	3
Reporter Type		
	Healthcare Professional	17

Appendix II. Summary of Demographics and Characteristics of AERS Chlorpheniramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=63)		
	Consumer	43
	Unknown	3
Type of Report		
	15-Day	53
	Direct	10

[¥] Therapeutic blood levels of chlorpheniramine were considered as 0.01 – 0.02 mg/L, based on Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

[†] Product classification and type was determined based on trade name or per report

[‡] The drug name is the verbatim name provided by the reporter or as specified per report. If more than one cough and cold product was reported, only the primary cough and cold medication was included under reported drug name. Only one product per case was listed.

[§] The concomitant cough and cold medications include trade names or ingredients of concomitant cough and cold medications that were reported, excluding the primary cough and cold medication listed in the reported drug name. Cases may have reported more than one concomitant cough and cold medication.

[£] Other concomitant medications include all other non-cough and cold medications that were reported.

Appendix III. Summary of Demographics and Characteristics of AERS Diphenhydramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=83)		
Sex		
	Male	44
	Female	35
	Unknown	4
Age		
	0 – 2 months	9
	3 – 11 months	16
	12 – 23 months	14
	2 years	13
	3 – 5 years	31
	Median = 2 years	
	Range = 3 weeks – 5 years	
Indication		
	Accidental ingestion – 11	Malaise – 1
	Accidental overdose – 5	Nasal Congestion – 1
	Allergy – 10	Nausea – 1
	Cold – 3	Rash – 3
	Cough – 3	Respiratory disorder – 1
	Deliberate poisoning – 2	Rhinorrhea – 2
	Edema – 2	Sedation – 1
	Eczema – 1	Sinus infection – 1
	Hives – 3	Sleep problem – 1
	Insomnia – 2	Throat infection – 1
	Intentional overdose – 1	Unknown – 27
Each Dose		
	1 mg – 1	12.5 mg – 10
	3.125 mg – 2	18.75 mg – 2
	5 mg – 1	25 mg – 2
	6.25 mg – 4	100 mg – 1
	7.5 mg – 2	Unknown – 55
	9.375 mg – 3	
Time to onset		

Appendix III. Summary of Demographics and Characteristics of AERS Diphenhydramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=83)		
	1 dose – 14	2 weeks – 3
	2 doses – 6	3 years – 1
	1 day – 5	Unknown – 54
Drug levels[¥]		
	< 0.1 mg/L	1
	0.1 – 1 mg/L	3
	> 1 mg/L	10
Product Classification[†]		
	OTC	53
	Rx	0
	Unknown	30
Product Type[†]		
	Single ingredient	44
	Combination/multiple ingredients	11
	Unknown	28
Reported Drug Name[‡]		
	Benadryl – 16	Children's Benadryl Allergy Liquid – 21
	Benadryl 25 mg tablets – 1	Children's Benadryl Allergy/Cold Fastmelt – 1
	Benadryl 50 mg capsules – 2	Children's Benadryl Allergy/Sinus – 3
	Benadryl Allergy – 3	Children's Benadryl Dye Free Allergy Chewables – 1
	Benadryl Allergy/Sinus – 3	Children's Benadryl Dye Free Allergy Liquid – 6
	Benadryl Allergy/Sinus Fastmelt – 1	Children's Benadryl-D Allergy/Sinus Liquid – 1
	Benadryl Kapseals – 2	diphenhydramine – 12
	Benadryl Ultratabs – 1	diphenhydramine 25 mg tablets – 1
	Children's Benadryl Allergy Chewables – 1	Extra Strength Tylenol PM – 1
	Children's Benadryl Allergy Fastmelt – 5	Hydramine Cough Syrup – 1
Concomitant Cough and Cold Medications[§] (N=11)		
	chlorpheniramine – 2	Nyquil – 1
	decongestant/antiallergic (unspecified) – 1	PediaCare Infant's Decongestant – 2
	dextromethorphan – 2	phenylpropanolamine – 1
	Dimetapp – 2	pseudoephedrine – 2

Appendix III. Summary of Demographics and Characteristics of AERS Diphenhydramine Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=83)		
	doxylamine – 1	Ronatic (generic Rynatan) – 1
	guaifenesin – 1	
Other Concomitant Medications[£] (N=25)		
	acetaminophen – 10	Pulmicort – 1
	Amoxil – 1	prednisolone – 2
	benzocaine – 1	prednisone – 2
	Bactrim – 1	promethazine – 1
	Demerol – 1	ranitidine – 1
	Elidel – 1	Singulair – 1
	lorazepam – 1	steroid (unspecified) – 1
	methadone – 1	Xopenex – 1
	metoclopramide – 2	Zithromax – 2
	periactin – 1	Zyrtec – 3
	phenytoin – 1	
Outcome		
	Death	26
	Hospitalization	14
	Other	43
Receive Year		
	2002	6
	2003	12
	2004	8
	2005	30
	2006	22
	2007 (January to May 11)	5
Reporter Type		
	Healthcare Professional	25
	Consumer	57
	Unknown	1
Type of Report		
	15-Day	78
	Direct	1
	Periodic	4

[¥] Therapeutic blood levels of diphenhydramine were considered as 0.1 – 1 mg/L, based on Toxic Drug Concentrations. Office of the Chief Medical Examiner. Chapel Hill, NC 27713 Last Revision: May 22, 2003.

[†] Product classification and type was determined based on trade name or per report

[‡] The drug name is the verbatim name provided by the reporter or as specified per report. If more than one cough and cold product was reported, only the primary cough and cold medication was included under reported drug name. Only one product per case was listed.

[§] The concomitant cough and cold medications include trade names or ingredients of concomitant cough and cold medications that were reported, excluding the primary cough and cold medication listed in the reported drug name. Cases may have reported more than one concomitant cough and cold medication.

[£] Other concomitant medications include all other non-cough and cold medications that were reported.

Appendix IV. Summary of Demographics and Characteristics of AERS Dextromethorphan Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=105)		
Sex		
	Male	56
	Female	43
	Unknown	6
Age		
	0 – 2 months	16
	3 – 11 months	24
	12 – 23 months	17
	2 years	22
	3-5 years	26
	Median = 18 months	
	Range = 1 month – 5 years	
Indication		
	Accidental exposure – 12	Otitis media – 1
	Asthma – 1	Postnasal drip – 1
	Cold – 12	Rhinorrhea – 3
	Congestion – 7	RSV – 1
	Cough – 16	Sinus headache – 1
	Fever – 1	URI – 2
	Flu – 1	Unknown – 43
	Nasopharyngitis – 3	
Each Dose		
	≤ 1mg – 4	10 mg – 2
	1.25 mg – 10	12 mg – 2
	2 mg – 2	15 mg – 5
	2.5 mg – 6	22.5 mg – 1
	3.75 mg – 2	30 mg – 1
	5 mg – 13	50 mg – 1
	7.5 mg – 12	Unknown – 44
Time to onset		
	1 dose – 30	6 days – 2
	2 doses – 4	7 days – 2

Appendix IV. Summary of Demographics and Characteristics of AERS Dextromethorphan Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=105)		
	3 doses – 6	9 days – 1
	1 day – 5	> 2 weeks – 2
	2 days – 3	Unknown – 50
Drug levels[¥]		
	< 2.4 mcg/L	0
	2.4 – 207 mcg/L	9
	> 207 mcg/L	7
Product Classification[†]		
	OTC	82
	Rx	17
	Unknown	6
Product Type[†]		
	Single ingredient	7
	Combination/multiple ingredients	87
	Unknown	11
Reported Drug Name[‡]		
	Accuhist Pediatric Syrup – 1	PediaCare Infant's Decongestant and Cough – 24
	Atuss DR – 1	PediaCare Infant's Long Acting Cough Liquid – 2
	Benylin DM Pediatric Liquid – 1	Polytussin DM – 1
	Bromfed DM – 1	Promethazine DM – 1
	Carbaxefed DM RF – 4	Q-tussin Cough Formula – 1
	Carbofed DM drops – 1	Robitussin CF – 1
	Cardec DM – 1	Robitussin Pediatric Night Relief – 1
	Cardec DM drops – 1	Rondec oral drops – 1
	Delsym – 3	Rondec DM drops – 2
	dextromethorphan – 11	Sudafed Children's Cough and Cold Liquid – 1
	dextromethorphan/pseudoephedrine – 1	Tanafed DMX – 1
	Dimetapp – 1	Triaminic Cold and Cough – 5
	Nyquil Children's Cold/Cough Relief – 2	Triaminic Cold and Night Time Cough – 2
	PediaCare Children's Long Acting Cough Plus Cold – 7	Triaminic Cough and Sore Throat – 3
	PediaCare Children's Multi-Symptom Cold – 9	Tylenol Children's Plus Cold and Cough – 1

Appendix IV. Summary of Demographics and Characteristics of AERS Dextromethorphan Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=105)		
	PediaCare Children's Nightrest Cough and Cold Liquid – 7	Tylenol Infant's Cough and Cold – 2
	PediaCare Cough Plus Cold Chewables – 2	Viravan DM – 1
	PediaCare Cough/Cold Liquid – 1	
Concomitant Cough and Cold Medications[§] (N=17)		
	Benadryl Allergy – 1	ephedrine – 2
	brompheniramine – 2	guaifenesin – 1
	Carbaxefed DM RF – 1	pseudoephedrine – 9
	carbinoxamine – 3	Robitussin CF – 1
	chlorpheniramine – 3	Sudafed Pediatric – 1
	diphenhydramine – 2	Triaminic – 1
	doxylamine – 1	Triaminic Cold and Night Time Cough – 1
Other Concomitant Medications[£] (N=42)		
	acetaminophen – 18	loperamide – 1
	albuterol – 2	Macrogol (laxative)- 1
	amoxicillin – 1	metoclopramide – 4
	Anaprox – 1	multivitamin – 3
	antibiotic (unspecified) – 3	Nystatin – 1
	benzocaine – 1	oxcarbazepine – 1
	calcium supplement – 1	phenobarbital – 1
	clomipramine – 1	prednisolone – 1
	clonidine – 1	Pulmicort respule - 2
	cod liver oil – 1	saline mixture – 1
	Diflucan – 1	senna – 1
	Ex-Lax – 1	Seroquel – 1
	Flexagen – 1	Singulair – 1
	ibuprofen – 7	sodium chloride – 1
	immunizations – 1	valproic acid – 1
	lansoprazole – 1	Viaxin – 1
	levorphanol – 1	Zyrtec – 1
Outcome		
	Death	28
	Life Threatening	2

Appendix IV. Summary of Demographics and Characteristics of AERS Dextromethorphan Pediatric Serious Adverse Event Cases received between 1/1/2002 and 5/11/2007 (N=105)		
	Hospitalization	22
	Other	53
Receive Year		
	2002	7
	2003	20
	2004	16
	2005	21
	2006	33
	2007 (January to May 11)	8
Reporter Type		
	Healthcare Professional	24
	Consumer	78
	Unknown	3
Type of Report		
	15-Day	92
	Direct	13

[¥] Therapeutic blood levels of dextromethorphan were considered as 2.4 – 207 mcg/L, based on Dunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of Over-the-Counter Cough and Cold Medications. Pediatrics. Sept 2001;108;3.

[†] Product classification and type was determined based on trade name or per report

[‡] The drug name is the verbatim name provided by the reporter or as specified per report. If more than one cough and cold product was reported, only the primary cough and cold medication was included under reported drug name. Only one product per case was listed.

[§] The concomitant cough and cold medications include trade names or ingredients of concomitant cough and cold medications that were reported, excluding the primary cough and cold medication listed in the reported drug name. Cases may have reported more than one concomitant cough and cold medication.

[£] Other concomitant medications include all other non-cough and cold medications that were reported.

MEDICAL OFFICER'S REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products

FDA Docket No:	**2007P-0074**
Subject:	**Cold and Cough Products for Over-the-Counter (OTC) Use**
Sponsor:	**Baltimore City Health Department (BCHD)**
Drug name:	**OTC Cough and Cold Drug Products**
Submission dates:	**March 1, 2007 and May 2, 2007**
Date completed review:	**July 24, 2007**
Reviewer:	**Lolita A. Lopez, M.D.**

I. INTRODUCTION

This is a clinical review of efficacy and safety of cough and cold drug products for over-the-counter (OTC) use in pediatric patients based on reports in the medical literature. This review was initiated because of concerns raised about the safety of cold medications that led to the removal of unapproved carbinoxamine drug products from the market, and addresses some of the issues identified by a Citizen Petition submitted to the Agency regarding the use of cough and cold medications in children less than six years old.

On June 9, 2006, FDA took enforcement action to stop the manufacturing of unapproved carbinoxamine maleate (CM) containing products because of safety concerns focused on their use in children under 2 years of age. This action was based on the reported infant deaths while taking combination products containing CM. Only the single-ingredient CM products are FDA approved for the treatment of allergic symptoms in patients > 1 year of age, none of the combination products are approved for marketing.

On March 1, 2007, a Citizen's Petition was submitted through the Baltimore City Health Department (BCHD). The Citizen Petition requests the Commissioner of Food and Drugs to take the following actions with respect to 21 CFR 341, Final Monograph (FM) for Cold, Cough, Allergy, Bronchodilator, Antiasthmatic Drug Products for Over-the-Counter Human Use:

1. *Provide a statement to the public explaining that over-the-counter antitussive, expectorant, nasal decongestant, antihistamine and combination cough and cold products have not been shown to be safe and effective for the treatment*

of cough and cold in children under six years of age.

2. *Notify manufacturers of these products whose labeling (1) uses such terms as "infant" or "baby," or (2) displays images of children under the age of 6 that:*
    a. *Such marketing- is not supported by scientific evidence, and*
    b. *Manufacturers will be subject to enforcement action at any time.*

3. *Amend 21 CFR 341 to require that labeling for over-the-counter antitussive, expectorant, nasal decongestant, antihistamine, and combination cough and cold products state:*
    a. *These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold.*
    b. *These products should not be used for treatment of cough and cold in children under 6 years of age.*

A comprehensive review of the literature was performed to search for all published articles on cough and cold medicines in children, specifically for clinical studies that investigated efficacy and safety. The literature was searched for all published articles on cough and cold medicines in children using PUBMED, EMBASE and SCOPUS. In addition, the list of references to support the Citizen Petition was also obtained and an internet search was also conducted for relevant published reports on this topic.

II. BACKGROUND

Cold symptoms are frequent in preschool children and are becoming more prevalent as more of this young population participates in child care programs; the average number of colds per year is generally quoted as being 3 to 10.[1] OTC cough and cold medicines are commonly used in children to provide acute, temporary relief of common cold symptoms such as nasal congestion, rhinorrhea and cough. For symptom relief, patients may take a product that contains a single or a combination of the following pharmacologically active ingredients: nasal decongestants (e.g., pseudoephedrine, phenylephrine), antihistamines (e.g., diphenhydramine, chlorpheniramine, brompheniramine), cough suppressants (e.g., dextromethorphan) and expectorants (guiafenesin). See table A-2 in the Appendix section for a complete list of active ingredients found in cough and cold products. Some of the combination products also contain antipyretics or analgesics (e.g. acetaminophen, ibuprofen), but these active ingredients will not be discussed in detail in this document.

Decongestants are sympathomimetic agents that decrease nasal congestion by causing vasoconstriction and improve patency by reducing blood volume and swelling in the nasal mucosa and paranasal sinuses. Adverse events include tachycardia, irritability, agitation, sleeplessness, hypertension, anorexia, headache, nausea, vomiting, palpitations, dysrhythmias,

[1] Kelly L. Pediatric cough and cold preparations. Pediatrics in Review/American Academy of Pediatrics Apr. 2004; 25 (4): 115-123.

seizures, dystonic reactions (systemic) and drying of nasal membranes, nosebleeds, rebound nasal congestion (topical).[2]

Antihistamines block H-1 receptors on nasal vasculature and compete with histamine for receptor sites; these also have anticholinergic drying action on mucous membranes. The most frequent side effects of antihistamines are dry mouth, mydriasis and sedation. Following overdose with a first-generation H_1 antihistamine, patients typically present with central nervous system (CNS) depression and an anticholinergic syndrome. These include mydriasis, tachycardia, fever, dry mucous membranes, urinary retention, diminished bowel sounds, and disorientation, agitation, hallucinations, confusion, sedation, coma, seizures, hypertension, hyperthermia and dry, flushed skin.[3]

Dextromethorphan is one of the most common non-narcotic cough medicines; it is a narcotic analog.[4] It acts centrally to elevate the threshold for coughing; adverse reactions are generally mild and infrequent. This include drowsiness, dizziness, and fatigue which can occur with therapeutic dosage. Excessive dose or overdose may result in confusion, excitement, nervousness, restlessness, irritability, nausea/vomiting, slurred speech, stupor, ataxia, nystagmus, hyperexcitability, dystonia (e.g., dystonic reaction), coma, toxic psychosis (e.g., hallucinations) and changes in muscle reflexes, respiratory depression, tachycardia and seizures.[5]

Guaifenesin, an expectorant, is intended to help thin secretions to be better expelled from the respiratory tract. In general, adverse reactions to guaifenesin are infrequent and usually not serious. When given in high or excessive dosage, nausea, vomiting, diarrhea, and/or abdominal pain may occur. Drowsiness, dizziness, and headache occur rarely at therapeutic doses. Rash (unspecified) has also been reported with guaifenesin products and excessive use or dosage may result in nephrolithiasis.[6]

Commonly used cough and cold medications[7] (listed above) were classified as "generally recognized as safe and effective" for human use gained FDA approval through the OTC monograph process (Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products for Over-the-Counter Human Use, 21 CFR 341). Pediatric dosing for these ingredients was based on

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[2] Ibid.

[3] Goldfrank's Toxicologic Emergencies - 8th ed. 2006. http://online.statref.com/Document/Document.aspx?DocId=483&FxId=68&Scroll=5&Index=9&SessionId=A66C09I(LOTHNQVDP) accessed 9/11/07.

[4] Kelly L. Pediatric cough and cold preparations. Pediatrics in Review/American Academy of Pediatrics Apr. 2004; 25 (4): 115-123.

[5] Clinical Pharmacology Online (http://cpip.gsm.com/) accessed 8-17-07.

[6] Clinical Pharmacology Online (http://cpip.gsm.com/) accessed 8-17-07.

[7] Indications for **antihistamines** (341.72): Temporarily relieves runny nose, sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever (which may be followed by one or both of the following): or other upper respiratory allergies or allergic rhinitis.
Indications for **decongestants** (341.80): For the temporary relief of nasal congestion due to the common cold or a cold, hay fever, or other upper respiratory allergies; or reduces swelling of nasal passages.
Indications for **antitussives** (341.74): Temporarily relieves minor throat and/or bronchial irritation associated with a cold or the common cold or inhaled irritants; or temporarily relieve the intensity of cough to help you get to sleep.
Indications for **expectorant** (341.78): Helps loosen phlegm (mucus) and thin bronchial secretions to rid the bronchial passageways of bothersome mucus, or drain bronchial tubes, or make coughs more productive.

extrapolation from the adult dose and was calculated as a fraction of the usual adult dose based on the child's age (see table A-1 in the Appendix). The following is generally the dosing recommendation in children: 6 to 12 years of age - ½ of the adult dose; 2 to 6 years of age - ¼ of the adult dose; and under 2 years of age - ask a doctor. There is a professional labeling (provided to health professionals but not to the general public) for the use of antihistamines and antitussives in children under 6 years of age, the indication is similar to adults. Professional labeling is not on the "Drug Facts" label of cough and cold products. Health professionals can find professional labeling for these active ingredients in the in the Code of Federal Regulations (21 CFR 341.90) and from dosing charts provided by the manufacturer or from drug information handbooks.

Dose extrapolation was based on the assumption that the pathophysiology of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients. There are no dosing recommendations listed for children < 2 years old in the monograph. The labels for OTC cough and cold medicines direct consumers to ask a doctor for dosing directions for children <2 years old; hence, the dosing and use of these drugs is left to the discretion of the physician. Physicians extrapolate dosing in this population from adult doses and doses labeled for older children based on the weight or age of the child, or physicians refer to the manufacturer's dosing recommendations, textbooks, pediatric handbooks (e.g. The Harriet Lane Handbook) or other drug information handbooks.

III. LITERATURE REVIEW

The literature search resulted in a list of published articles that fall in one of the following categories which will be the focus of this review:

A. Clinical studies (controlled or non-controlled)
B. Case reports/series

In addition, the search also resulted in articles that reviewed clinical trials, descriptive articles, Guidelines and/or Policy Statements from Professional Organizations, and publications or reports related to the use of these medications.

A. Clinical Studies in Children

(For a tabulated summary of the characteristics of clinical studies, see table A-3 in the Appendix)

1) Paul IM, Yoder KE, Crowell KR, et.al.
Effect of Dextromethorphan, Diphenhydramine, and Placebo on Nocturnal Cough and Sleep Quality for Coughing Children and Their Parents
Pediatrics 2004;114:e85–e90. (http://www.pediatrics.org/cgi/content/full/114/1/e85)

The objective of the study was to determine whether dextromethorphan or diphenhydramine administered to children with acute cough as a result of URIs subjectively improves nocturnal cough when compared to placebo.

Study Design and Methods: This was a single-dose, double-blind, randomized study in 100 children (2 to 18 years old) with upper respiratory infections (URI) for ≤7 days. Patients were excluded if they had signs or symptoms of more treatable diseases (e.g., asthma, pneumonia, allergic rhinitis, infection) or chronic lung disease. Parents were questioned to assess (for both child and parent) the frequency, severity, and bothersome nature of the nocturnal cough for two nights. After stratification for age (2–5 years, 6–11 years, 12–18 years), each child was randomly assigned in a double-masked manner to receive a single-dose of one of the 3 treatments for one night:

- Dextromethorphan (Benylin®) (DM)
  Dosage for DM was based on the label recommendations in children:
  - 2 to 5 y/o=7.5 mg/dose
  - 6 to 11 y/o=15 mg/dose
  - 12 to 18 y/o=30 mg/dose.
- Diphenhydramine (Diphen AF®) (DPH)
  - dosed by weight at 1.25 mg/kg/dose (maximum 50 mg/dose)
- Placebo (Simple syrup NF).

Parents were instructed to administer the medication 30 minutes before the child was to go to sleep. A second survey asking the same questions was then administered the following day to assess symptom severity for the night when treatment was given. Subjective parental assessments of cough and sleep difficulty were assessed using a 7-point Likert scale for two days (see survey questions below). The range of cough frequency ranged from "constant" (equal to 6 points) to "not at all" (equal to 0 points); questions related to impact on ability to sleep, severity of cough, and bothersome nature of the cough ranged from "extremely" (6 points) to "not at all" (0 points). Only parents who answered at least "somewhat" (3 points) for a minimum of 2 of 3 questions related to nocturnal cough frequency, impact on the child's sleep, and impact on parental sleep were eligible.

The principle outcome measure of interest was frequency of cough. Change in cough severity, the impact of the cough on sleep for both child and parent, and the bothersome nature of the cough for the child and the parent all were secondary outcome measures of importance. Treatment group comparisons were conducted by 1-way analysis of variance. Fisher exact tests were used to compare adverse reaction rates between treatments. The between-night change in individual outcomes and the combined symptom score were evaluated using paired t tests for the entire cohort.

Survey questions to assess nocturnal cough and sleep difficulty

1) How frequent was your child's cough last night?
o Constant o Very Much o A lot o Somewhat o A little o Occasional o Not at all

2) How much did last night's cough affect your child's ability to sleep?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

3) How much did last night's cough affect your ability to sleep?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

4) How severe was your child's cough last night?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

5) How bothersome was last night's cough to your child?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

Results: A total of 100 children with URIs were enrolled and completed the single-night study: 33 received diphenhydramine, 33 received dextromethorphan, and 34 received placebo. Symptom scores were obtained on the night before enrollment and were compared with scores from the subsequent nights when medications were given. All outcomes showed improvement. The scores for cough frequency, impact on child and parent sleep, "bothersome" nature of cough, and severity of cough all were scored significantly lower on the second night ($P<0.0001$). The mean combined symptom score was reduced from 19.83 to 8.93 (95% confidence interval for reduction: 9.38–12.42; $P<0.0001$). When separated by treatment group, no significant differences were found for any outcome measures when comparing the 3 treatment groups. When the results for these 5 outcomes were combined, there was no significant difference between treatments. The children in the DPH treatment group improved by an average of 11.79 points compared with 10.06 for DM and 10.85 for PL ($P=.62$). Neither diphenhydramine nor dextromethorphan produced a superior benefit when compared with placebo for any of the outcomes studied.

- Cough frequency: Those who received DPH and DM had a mean 1.97-point improvement compared with a mean 2.24-point change for the better in those who received PL ($P=.56$).
- Child's sleep quality: Better for those who received DPH with a mean improvement of 2.64 points compared with 1.88 points for DM and 2.18 points for PL, but this result did not achieve statistical significance ($P=.28$).
- Parental sleep: Changes of 2.67 points for the DPH arm and 2.45 and 2.59 points for DM and PL, respectively ($P=.85$).
- In all treatment arms, parents believed that cough was less bothersome to their children, with improvements of 2.45 points for those who took DPH, 1.91 points for those who got DM, and 1.97 points for those in the PL arm ($P=.29$).
- Severity of their child's cough: Parents also noted similar improvements in the severity of their child's cough regardless of treatment: 2.06 points with DPH, 1.85 points with DM, and 1.88 points with PL ($P=.70$).

Adverse effect: The most commonly reported reaction was hyperactivity (DPH-3, DM-6, PL-5), which was reported for 14 children (14%); there was no significant difference between the treatment arms, including placebo. The only 2 adverse reactions that

approached statistical significance were insomnia in the DM group (3) p=.07) and drowsiness in the DPH group (3) (p=.07). Other adverse events were: disorientation (PL-1), dizziness (DM-1), headache (DPH-1), nervousness (DPH, DM, 1-each), stomachache/nausea (DPH-1, DM-2, PL-3).

Study Authors' Conclusions. DPH and DM are not superior to placebo in providing nocturnal symptom relief for children with cough and sleep difficulty as a result of a URI. The medications given to children do not result in improved quality of sleep for their parents when compared with placebo. Each clinician should consider these findings, the potential for adverse effects, and the individual and cumulative costs of the drugs before recommending them to families.

Comments:

- *The dose for DM was consistent with the monograph dosing; however, the dosing frequency was not consistent with the monograph. DPH dose was weight-based which was not consistent with the monograph dosing; DPH is labeled for use every 4 hours (see table A-2). It was not specified how many hours patients were evaluated. In a span of 8 to 10 hours sleeping time, ideally, the child should have received 2 doses of the active treatment; therefore, a single-dose may not have been adequate to elicit the effect of the drug or show the difference from placebo.*
- *Parents who answered at least "somewhat" (3 points) for a minimum of 2 of 3 questions related to nocturnal cough frequency, impact on the child's sleep, and impact on parental sleep were eligible for enrollment into the study. The study does not include very ill patients; this may also make difficult to demonstrate a difference in the effect of the active ingredients.*
- *The "frequency of cough" is an appropriate primary endpoint to measure. However, the scale used to rate the frequency as well as severity of cough were not defined. For example, in assessing frequency of cough, "very much" vs. "a lot", and "a little" vs. "occasional" are difficult to distinguish from each other. In addition, cough is a symptom that can be measured objectively. Therefore, a self/parent rated score to measure a primary endpoint is very subjective and imprecise. Ideally, the frequency of cough should be defined by the number of cough episodes over a short duration time (e.g., number of cough episodes every hour or every 4 hours).*
- *The timing of evaluation of the effect of the test drug should occur when the efficacy of the drug is expected to occur (e.g., within 4 hours).*
- *The effect of cough on the parent and child's ability to sleep is not related to either test drug's therapeutic effect.*
- *It was not described how a parent monitored the child's cough.*
- *Compliance was not guaranteed in this study. Therefore it is unknown how many patients took the drug as directed.*
- *It was not specified how many patients were in each subgroup (2-5 y/o, 6-11 y/o, 12-18 y/o), the subjects were predominantly white (76-82%) and the number of patients in each treatment arm is small (n=33 to 34).*

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?
The Journal of Pediatrics, Vol.130 (3), March 1997, pp 463-466.

The objective of the study was to determine whether an antihistamine-decongestant combination (ADC) is superior to placebo in temporarily relieving symptoms of upper respiratory tract infection (URI) in preschool children.

Design and Methods: This was a randomized, double-blind, placebo-controlled trial in 59 children, 6 months to 5 y/o with URI of <7 days. Patients were excluded if they had history of asthma or allergies or were currently taking any prescribed medication at the time of diagnosis. Children were randomly assigned in a double-blind fashion to receive one of the following[8] *as needed* for URI symptoms for 48 hours up to 4 doses:

- ADC (Dimetapp® Elixir: each 5 ml contains brompheniramine maleate 2 mg/5ml + PPA[9] 12.5 mg)
    - 6 mos. old - 2 y/o: ½ tsp q 4 hrs.
    - 2 y/o - 5 y/o: 1 tsp q 4 hrs.
- Placebo

Two hours after each dose, changes in the child's runny nose, nasal congestion, cough, and sleep status were assessed by means of a standardized questionnaire. A 7-point Likert scale that ranged from "much worse" to "much better" was used. Parents also recorded whether or not the child was sleeping. Only acetaminophen was allowed as concomitant medication.

Results: A total of 175 responses were recorded for 59 patients (n=28 ADC, n=31 placebo). Results show that there was no statistically significant differences between the ADC and the placebo group with regard to the proportion of children showing improvement in the symptoms of runny nose (p=0.48), nasal congestion (p=0.94), and cough (p=0.66). Similarly, comparison of individual Likert scale scores showed no significant differences with regard to changes in any of the symptoms between the two groups. The proportion of children asleep 2 hours after receiving the ADC was significantly higher than placebo (46.6% vs. 26.5%; p = 0.01).

Adverse Events: No information on adverse events was provided in this study.

Study Authors' Conclusion: ADC was equivalent to placebo in providing temporary relief of URI symptoms in preschool children and ADC had significantly greater sedative effects compared to placebo. One potential explanation for the continued frequent use of these medications may be their sedative side effects; parents may view the sedative quality of an ADC as a desirable one.

[8] Dosing was from a standard drug reference: Benitz WE, Tatro DS, editors. The pediatric drug handbook, 3rd ed. St. Louis: Mosby-Year Book, 1995:62.
[9] PPA-phenylpropanolamine maleate is no longer marketed in the U.S.

Comments:

- *The dosing frequency of every 4 hours for brompheniramine was consistent with the monograph; however, the dose was not consistent with the monograph. A dose of 2 mg every 4-6 hours was used in the study which was double the recommended dose of 1 mg every 4-6 hours in the monograph (see table A-2). The medication was also taken on a "as needed" dosing schedule which means that patients waited for symptoms to re-dose, this may not be a good way to evaluate a treatment effect.*
- *Unlike runny nose and nasal congestion, cough is a symptom that would not likely benefit from this antihistamine-decongestant (brompheniramine-PPA) combination. Therefore, the ADC may not be expected to show efficacy in relieving cough.*
- *The assessment of symptoms two hours after each dose was appropriate as treatment effect may occur within this time period.*
- *The full categories in the symptom rating scale were not provided and were not defined in the study.*
- *The severity of each symptom was not provided at baseline and the definition of each symptom improvement was not provided.*
- *The mean age of the patient is 24 months in the ADC group and 30 months in the placebo group, it is not specified how many patients were in each age range; the number of subjects in this study is also small. The authors recognize that the patient population was predominantly middle-class, white, privately insured group, which may limit generalizability of the results.*
- *There was an increase in the proportion of children asleep after taking the drug. However, it was not clear if this meant that patients had improved symptoms and were able to sleep better or is this due to sedation which is a common side effect from taking antihistamines. No further clarification was provided for this result obtained in the study.*
- *There were no adverse events mentioned in the study, although sedation should be considered a side effect. As stated by the authors, parents may view the sedative quality of an ADC as a desirable side effect.*
- *Despite the doubling of the dose of brompheniramine in this study, there were no reports of serious adverse events provided.*

3) Taylor JA, Novack AH, Almquist JR, Rogers JE.
Efficacy of cough suppressants in children.
J Pediatr 1993; 122:799-802.

The objective of this study was to test the hypothesis that codeine and dextromethorphan are effective in alleviating the symptoms of acute cough.

Design and Methods: This is a randomized, controlled trial in 57 children 18 months to 12 years old seen in private pediatric practices with significant night cough (prolonged or often, >10 coughs during the night) of < 14 days duration. Patients were excluded if they had a history of underlying lung disease, reactive airway or taking antibiotics or bronchodilators. Patients were randomly selected to receive one of following identical appearing medications at bedtime for 3 nights:

- Guaifenesin 100 mg + dextromethorphan 15 mg, per 5 ml (DM)
- Guaifenesin 100 mg + codeine 10 mg, per 5 ml (codeine)
- Placebo (cherry syrup)

Dose: 18 months to 5 y/o = 2.5 ml; 6 to 12 y/o = 5 ml[10]

The following morning, parents rated the amount of coughing and the loss of sleep because of coughing and noted any postussive emesis in their child during the previous night, on a form. After the last day of the study, parents noted any side effects in their child. Cough was scored (range 0=none to 4=very often) for each day and at baseline. Composite symptom score (css) were also calculated by adding the cough score, loss of sleep score, and posttussive emesis score (range for css: 0 to 9) computed for each day of the study.

Results: A total of 57 patients were enrolled, data were available on 49 patients: placebo=13, DM =19, and codeine=17. Cough and composite symptom scores improved in each group on each day of the study, with no significant difference between placebo and either DM or codeine on any day, see table 1. Neither dextromethorphan nor codeine (in combination with guaifenesin) was significantly more effective than placebo in reducing cough ($p = 0.41$ and 0.70, respectively). Reduction in cough score was correlated with the severity of cough at the start of treatment ($p = 0.007$), the most marked decrease in cough score occurred in children with the most severe cough at the start of the study. Regardless of treatment group, the cough score decreased significantly on day 3 of the study (coefficient = 0.87; $p < 0.0002$).

Table 1. Mean reduction in cough scores and composite symptom scores from baseline in each treatment group

Day of study	Codeine	*p*	Placebo	*p*	DM
Reduction in cough scores					
1	1.1	0.67	1.2	0.80	1.4
2	1.5	0.89	1.6	0.74	1.5
3	2.2	0.52	2.2	0.97	2.1
Reduction in composite symptom scores					
1	1.9	0.52	2.4	0.65	2.6
2	2.5	0.26	3.3	0.56	3.0
3	3.9	0.76	4.3	0.56	3.8

The p values are for comparisons between adjacent treatment groups.

Adverse Events: Side effects were reported in 18 patients, including 7/13 children in the placebo group, 6/19 receiving DM, and 5/17 codeine recipients. Drowsiness (3-placebo, 3-DM), diarrhea (3-placebo, 1-codeine, 1-DM), hyperactive behavior (2-DM, 3-codeine) were reported.

Study Authors' Conclusion: Neither codeine with guaifenesin nor DM with guaifenesin is superior to placebo in alleviating the symptoms of acute night cough in children. The two medications and placebo were virtually identical in efficacy regardless of the outcome measure employed, and by three days after a visit to a pediatrician due to cough symptoms,

[10] Doses were based on recommendations published in a text on drug therapy: AMA drug evaluations. 5th ed. Philadelphia: WB Saunders, 1993:561-4.

cough will be significantly reduced regardless of specific therapy. This reduction was most noticeable in children whose coughing symptoms are the most severe at the start of treatment.

Comments:

- *The dextromethorphan and guaifenesin dosing were consistent with the monograph for children who are 2 to 12 y/o. The monograph dosing for codeine was not followed in this study; the monograph does not recommended use of codeine in children <2y/o. (See table A-1).*
- *Patients received a single-dose of each medication at bedtime. It was not specified how many hours patients were evaluated. In a span of 8 to 10 hours of sleeping time, ideally, the child should have received 2 doses of the active treatment; therefore, a single-dose may not have been adequate to elicit the overnight effect of the drug or show the difference from placebo.*
- *It would be useful to assess symptoms around two hours after each dose as treatment effect may occur within this time period.*
- *The study stated that composite symptom scores were also calculated by adding the cough score, loss of sleep score and posttussive emesis score (range: 0 to 9) computed for each day of the study. Cough was scored (range 0=none to 4=very often) for each day and at baseline. It is not clear why the range for composite symptom score is 0 to 9 and not 0 to 12 as expected.*
- *The "amount of coughing" is an appropriate outcome to measure. However, it is not clear how either of the test drug is expected to show efficacy in assessing loss of sleep because of coughing and postussive emesis.*
- *It is desirable to have eligibility criteria with regard to the number of coughs over a duration of time. However, an eligibility criteria of "one prolonged coughing episode or at least 10 to 20 coughs (1-2 coughs/hr) during the night" might not be severe or frequent enough to detect treatment effect.*
- *Cough is a symptom that can be measured objectively, therefore, self/parent rated subjective scoring will be imprecise. Ideally, the frequency of cough should be defined by the number of cough episodes over a short duration time (e.g., number of cough episodes every hour or every 4 hours).*
- *Although patients were assessed at baseline, baseline symptom scores were not provided.*
- *The full cough rating scale was not provided; the scale used to rate cough were not defined or quantified in the study. It was not specified if the scale for assessing cough is validated.*
- *Even though it is stated that patients with underlying lung disease such as cystic fibrosis were excluded, it is not specified if patients were evaluated for other etiologies of nocturnal cough such as reflux.*
- *The number of patients in the study arm is small (13 to 19).*

4) **Hutton N, Wilson MH, Mellits ED, et al.**
Effectiveness of an antihistamine-decongestant combination for young children with the common cold: A randomized, controlled clinical trial
The Journal of Pediatrics Vol 118(1), January 1991, pp 125-130.

The objectives of the study were to determine:

- the proportion of parents with a young child with upper respiratory infections (URI) symptoms who believe that a medicine is needed for treatment of those symptoms.
- the effectiveness of an antihistamine-decongestant combination for symptomatic relief in young children with the common cold.
- whether parental assessment of improvement at 48 hours is associated with whether medication was desired and received.

Design and Methods: This was a randomized, controlled clinical trial in 96 inner city children 6 months to 5 y/o with URI symptoms with no serious or treatable disease (e.g., T >38.9° C, wheezing, antibiotics prescribed). Patients were randomized to one of the following treatment 3x/day for two days:

- Drug: Dimetapp®: antihistamine-decongestant fixed combination per 5 ml:
  - Brompheniramine maleate (4 mg)
  - Phenylephrine HCl (5 mg)
  - Phenylpropanolamine HCl (5 mg)

  Dosage: calculated by weight to achieve a brompheniramine dosage of 0.5 to 0.75 mg/kg/day, divided 3x/day
- Placebo
- No treatment

Neither parents nor investigators were aware of the drug-placebo assignment; however, parents of those who received no medicine were aware of their no-treatment status to measure any placebo effect of receiving a medication. Parents were interviewed using a standardized questionnaire about the nature and duration of the child's symptoms and whether he/she thought that the child needed medication. Adults were asked to rate the child's condition in the past 24 hours for nine symptoms (see table 2) commonly associated with URI and scored as either: 0 (not at all), 1 (occasionally), 2 (frequently), or 3 (all the time). Improvement was defined as a positive change in the symptom severity ratings. The behavioral symptoms (decreased appetite, crankiness, sleep disturbance, and excessive sleepiness) were also included. A follow-up interview was conducted 48 hours after the visit to evaluate the child's overall status and symptoms. Outcomes for each symptom and for the parent's overall rating were calculated by subtracting the severity scores at follow-up from the corresponding score at enrollment. This gave a range of possible changes from -3 (symptom not present initially, now occurs all the time) to +3 (symptom was occurring all the time, now not at all). Improvement was defined as a positive change in the symptom severity ratings. Parents also were asked whether they thought that there were side effects or benefits from the study medication.

Results: The population studied was primarily black, lived in the inner city and was of low socioeconomic status. Initial interviews were completed for 371 children; 239 (64%) were

excluded by the predetermined eligibility criteria, most often due to use of antibiotics. Of the 132 eligible children, 36 parents did not participate (9 left the clinic before being asked about the study and 27 refused participation) and 96 (73%) were randomized: drug=36, placebo=27, no medication=33. Final interviews were completed for: 30 (83%) of the drug group, 24 (89%) of the placebo group, 30 (91%) of the no-treatment group. Children in the no-treatment group were significantly more likely to have received other medicines during the study period than children who received either the drug or placebo (no treatment, 9/30; drug, 3/30; placebo, 0/24; $p<0.05$). Acetaminophen use was most commonly reported, drug group=3 and no-treatment group=7; in addition, within the latter group: OTC cold remedy=1, cough medicine=1, laxative=1.

Approximately 2/3 of study parents believed that their children needed medicine for cold symptoms (61 to 70%). By the parents' overall impression, 64% of the children were considered better at 48 hours. Within treatment groups this included: drug group= 20/30 (67%), placebo=17/24 (71%), no medicine=17/30 (71%). The proportion reporting improvement for each symptom were compared; there were no significant differences among the groups, except for the symptom of congested or runny nose, for which a significantly larger proportion of the placebo-treated group improved compared with the drug or no-medicine group. Also, there were no significant differences among the three treatment groups in the standardized severity changes (z scores) for either individual symptoms or for all nine symptoms combined (when analysis of variance was used).

Parental initial assessment of the need for medicine was a strong predictor of the degree to which symptoms were said to have changed. Improvement in symptoms in children whose parents wanted medicine was greater than in those whose parents had not wanted medicine.

Table 2. Number and percentage of parents reporting improvement in children, by symptom and treatment allocation

	No. of parents (%)		
	Drug (n = 30)	Placebo (n = 24)	No treatment (n = 30)
"Better" overall 2 days after visit	20 (67)	17 (71)	17 (57)
Positive rating change (improvement)			
Congested or runny nose*	16 (53)	19 (79)	14 (47)
Breathing problems	7 (23)	8 (33)	9 (30)
Fever	13 (43)	12 (50)	9 (30)
Cough	20 (67)	14 (58)	21 (70)
Decreased appetite	14 (48)	9 (38)	12 (40)
Crankiness	14 (48)	15 (62)	12 (40)
Sleeping disturbance	18 (60)	12 (50)	15 (50)
Excessive sleepiness	12 (40)	6 (26)	8 (27)
Vomiting	2 (7)	3 (13)	2 (7)

*$p < 0.05$.

Parental initial assessment of the need for medicine was a strong predictor of the degree to which symptoms were said to have changed.

Adverse Events: The side effects reported were: loose stools (1-placebo), hyperactivity (1-drug), sleepier than usual (1-drug); the latter was considered by parents as a benefit.

Study Authors' Conclusion: There was no difference in parental report of improvement among children receiving an antihistamine-decongestant combination (ADC), a placebo, or no medicine; more than half of the children were considered better 2 days after their visit no matter how they were managed. The majority (2/3) of parents believed that their children needed medicine for the common cold. Parents who believed that their children needed medicine reported greater improvement at 48 hours than those who did not want medicine, regardless of the treatment assigned. The results of this study do not support the common practice of prescribing an antihistamine-decongestant preparation for young children with the common cold.

Comments:

- *All except one (congested or runny nose) of the symptoms evaluated were unlikely to benefit from the therapy, this may affect composite score. An antihistamine-decongestant combination is not expected to treat the rest of the symptoms evaluated in the study.*
- *The distribution of baseline symptom scores was not provided. The distribution of post treatment improvement scores was not provided as well; this could be useful to see how they improved from baseline.*
- *The severity of baseline symptoms was not provided, it was only stated that there was no difference between the groups. It would be useful to see how much symptoms improved from baseline.*
- *A symptom improvement in the study required only a change of one category. Since the definition of success was not difficult to reach, it may have been difficult to show a treatment effect compared to placebo.*
- *The dosing frequency of 3x/day for this antihistamine-decongestant combination as well as the weight-based dosing used in the study is not consistent with the monograph. The dosing regimen for brompheniramine should be 1 mg every 4 to 6 hours (not to exceed 6 mg/24 hours) (see table A-2). A dosing of 3x a day may not be adequate to elicit the expected effect of the drug.*
- *The time interval from initiation of therapy to the follow-up interview after 48 hours was too long; this may affect efficacy measurement. The timing of evaluation of the effect of the test drug should occur when the efficacy of the drug is expected to occur; the study did not take into consideration that treatment effect may occur within an hour after treatment.*
- *It would be useful to measure symptoms more frequently than once during the 48-hour time period.*
- *Approximately 20% of the population received less than the prescribed amount and 9 to 17% of patients were lost to follow-up. Both of these may affect efficacy of the test drug.*
- *The population studied was primarily black, lived in inner city and was of low socioeconomic status, and the number of patients in each treatment arm was small (27 to 36 patients, N=96); these limit the generalizability of the study results.*
- *The no treatment effect suggests that the illness is improving with time.*

5) Korppi M, Laurikainen K, Pietikainen M, and Silvasti M.
Antitussives in the treatment of acute transient cough in children
Acta Paediatr Scand 1991 Vol. 80 (10); 969-71.

The objective of the study was to compare the efficacy of two preparations, an antitussive or an antitussive/β_2 sympathomimetic combination, with that of placebo in the treatment of cough related to acute respiratory infection in children.

Design and Methods: This was a double-blind parallel group study in 78 children ages 1-10 y/o with respiratory infection associated with cough. Excluded were patients with cardiac, hepatic, renal or bronchial disease. Patients were randomly divided into three treatment groups:

- Dextromethorphan 1.5 mg/ml (D)
- Dextromethorphan 1.5 mg/ml + salbutamol 0.2 mg/ml combination (DS)
- Placebo mixture (P): identical to the base mixtures used in active medicaments.

The treatment was given 3x/day for 3 days. The dosage was: <7 y/o = 5 ml; >7 y/o = 10 ml.

No other expectorants, antitussives, antihistamines or bronchodilators were allowed during the study. Antibacterial therapy was used if clinically indicated. During the treatment period the following symptoms were recorded daily by the parents: frequency and severity of cough during the day and night using a scale from 0 to 3 (0=no, 1=mild, 2=moderate, and 3=severe symptoms). General conditions of the patients were also recorded daily using a scale from 0 to 3 (0=worse, 1=the same as, 2=better and 3=much better than before the treatment). At the end of the treatment period the overall benefit of the medication was evaluated by the parents using alternatives *(verbatim from original article):* marked, some or no relief. Side effects (tremor, palpitation, restlessness, insomnia, tiredness, nausea, vomiting, gastric discomfort, dysuria and headache) were recorded using a scale from 0 to 2 (0=no, 1 =mild and 2 =severe side effects).

Results: A total of 75 patients completed the study: D=24, DS=25, P=26. Scores for each of the four cough symptoms dropped significantly in all three groups during the study period but no difference was found between the study groups on any of the three days. The same observation was made concerning the general condition recorded by the parents. More than half of the patients (56 % in DS-group, 66 % in D-group and 73 % in P-group) reported some or marked relief by the medication. The differences between the groups were not statistically significant.

Adverse events: The incidence of side effects was low and equal in the treatment and control groups. Tremor, which is a known side effect of salbutamol, was seen in only one patient in the DS-group. There were a total of 7 side effects documented, 3 on each D, and DS group, and 1 for the placebo group but no details on these were provided.

Table 3. Mean scores (SD) of the 4 cough symptom scores recorded during the study

	DS-group (n=25)	D-group (n=24)	P-group (n=26)
1. Cough symptoms			
Before treatment	1.75 (0.45)	1.66 (0.47)	1.81 (0.32)
1st treatment day	1.61 (0.45)	1.30 (0.59)	1.44 (0.43)
2nd treatment day	1.11 (0.56)	0.93 (0.59)	1.06 (0.55)
3rd treatment day	0.88 (0.56)	0.60 (0.48)	0.76 (0.62)
2. General condition			
1st treatment day	0.92 (0.41)	1.00 (0.51)	1.40 (0.50)
2nd treatment day	1.35 (0.57)	1.48 (0.73)	1.64 (0.57)
3rd treatment day	1.75 (0.61)	2.00 (0.78)	2.08 (0.80)
3. Number of patients reporting relief by the medication			
Some or marked relief	14	16	19
No relief	8	3	5
Cannot say	3	5	2
4. Number of patients reporting side effects			
Mild side effects	5	9	11
Severe side effects	3	3	1

Difference between groups: not significant, Kruskal-Wallis anova (1, 2) and χ^2 test (3).

Study Authors' Conclusion: The results of the present study support the view that cough associated with acute respiratory infection is self-limiting and antitussives should not be routinely used in the treatment of cough in children with acute viral infection. In addition, the suggested efficacy of the antitussives in the treatment of cough during nights cannot be confirmed. The use of antitussives should be restricted to situations where their efficacy has been proven, i.e. in the treatment of chronic non-productive cough.

Comments:

- *Cough at baseline and after treatment were assessed; this was appropriate. However, the severity of the illness at baseline was not provided.*
- *The dose was consistent with the monograph dose except for patients who are 6 to 7 y/o who should have received 15 mg instead of 7.5 mg of dextromethorphan. The dosing frequency for dextromethorphan is every 4, 6 or 8 hours (see table A-2) depending on the dose. It is not clear if and how a dosing of 3x/day was defined for the parents, this can be interpreted as every 4 to every 8 hours.*
- *The scale used to assess the severity and frequency of cough in this study was not defined for the parent. Cough is a symptom that can be measured objectively, therefore, self/parent rated symptom scoring is very subjective and imprecise. Ideally, the frequency of cough should be defined by the number of cough episodes over a short duration time (e.g., number of cough episodes every hour or every 4 hours).*
- *It was stated that symptoms of cough were recorded daily, it is assumed that this occurred once a day but the timing of assessment was not specified. The timing of evaluation of the effect of the drug should occur when the efficacy of the drug is expected to occur. Assessment of symptoms once a day may not be adequate, measuring symptoms more frequently would be useful.*

- *The alternatives in the evaluation of the overall benefit of the drug, specifically, "marked relief" was not defined.*
- *Antibiotics use was allowed in this study which is a potential confounding factor; the article did not provide any information as to how many patients in the study were actually prescribed antibiotics.*
- *Salbutamol is a bronchodilator not available for OTC use in the United States and is not indicated for the relief of acute cough due to the common cold.*
- *It is not clear how symptoms were assessed accurately during the night when the parents are expected to be asleep.*
- *Side effects should have been categorized as: none, mild, moderate or severe (moderate was not included in the categories used).*
- *The number of the patients in each treatment arm is small (n=24 to 26).*
- *This study was conducted in Finland, the characteristic of the population studied was not provided, it is uncertain if the result of the study can be generalized to the U.S. population.*

6) Sakchainanont B, Chantarojanasiri T, Ruangkanchanasetr S, et al.
Effectiveness of Antihistamines in Common Cold.
J Med Assoc Thai, Feb 1990; 73(2): 96-101

The objective of this study was to investigate the effect of the two antihistamines, namely, clemastine fumarate and chlorpheniramine maleate compared with placebo.

Design and Methods: This was a double-blind, randomized, and controlled study to investigate the effect of the two antihistamines: clemastine fumarate (CF) and chlorpheniramine maleate (CM) compared with placebo in 143 patients aged 1.5 months to 5 years from the pediatric out-patients in a hospital in Thailand. Included were patients who had rhinorrhea with or without occasional non-productive cough of 3 days duration, fever < 38.3°C (100.9°F). Patients who had history of allergy or bacterial infection were excluded. Patients were randomly allocated into 3 groups:

- Group I - clemastine fumarate 0.05 mg/kg/day, 2x/day (am, evening).
- Group II - chlorpheniramine maleate syrup 0.35 mg/kg/day, 3x/day (am, late pm, before bedtime).
- Group III - placebo 2 or 3x/ day, the control group.

All medications were prepared in equal volumes of 0.5 ml/kg/dose so that both parents and physician were blinded. Patients were evaluated daily by parents; and the investigator before treatment and 3 days after treatment using the symptom score: 3=severe, 2=moderate, 1=mild, 0= free of symptoms. The outcome, derived from the difference of the score (pre-treatment minus post-treatment score), was compared on a 5 level rating: worse = -1 to -3, no change of symptoms = 0, improved = 1 to 3. The following symptoms were evaluated: nasal discharge (frequency, character, amount), cough and swelling of nasal turbinates. The character of nasal discharge was scored as: no secretion=0, dry nose=1, white and thick=2 and clear=3.

Results: There were 143 patients that completed the study: Group I=48, Group II=48, Placebo=47. There was a statistically significant improvement of every symptom in every group including placebo. When these improvements were compared simultaneously, the character of nasal discharge was statistically significant (p = 0.0143) compared to baseline. See table below. Further, clemastine and chlorpheniramine improved the character of nasal discharge compared to placebo, p=0.008 and p=.0172, respectively. However, the effects of these two antihistamines were not different. Other than character of nasal discharge, there were no differences in improvement of symptoms from baseline among the three groups.

Adverse events: Slight drowsiness and sleepiness were the side effects evaluated in this study. There was no difference in the adverse effects among the groups, but the degree of sleepiness was increased more than degree of slight drowsiness after treatment. The authors state that this might indicate that when patients had improved, they slept longer and better.

Table 4: Distribution of symptoms and signs of patients before treatment

Variable	(score)	Clemastine fumarate (N = 48) (%)	Chlorpheniramine maleate (N = 48) (%)	Placebo (N = 47) (%)	P value**
1. Nasal discharge					
–Frequency	no secretion (0)	1 (2.1)	–	–	0.7765
	sometimes (1)	2 (4.2)	–	4 (8.5)	
	often (2)	28 (58.3)	24 (50)	24 (51.1)	
	always (3)	17 (35.4)	24 (50)	19 (40.4)	
–Character	no secretion (0)	–	–	–	0.2460
	dry nose (1)	1 (2.1)	–	–	
	white & thick (2)	7 (14.5)	5 (10.4)	11 (23.4)	
	clear (3)	40 (83.3)	43 (89.6)	36 (76.6)	
–Amount	no secretion (0)	1 (2.1)	–	–	0.2534
	dry nostrils (1)	1 (2.1)	3 (6.3)	6 (12.7)	
	secretion in nostrils (2)	32 (66.6)	32 (66.6)	32 (68.1)	
	secretion from nostrils (3)	14 (29.2)	13 (27.1)	9 (19.1)	
2. Cough					
	no cough (0)	3 (6.3)	4 (8.3)	3 (6.3)	0.6076
	sometimes (1)	10 (20.8)	9 (18.7)	5 (10.6)	
	often (2)	35 (72.9)	31 (64.6)	36 (82.9)	
	always (3)	–	4 (8.3)	–	
3. Turbinates					
	no edema (0)	12 (25)	15 (31.2)	18 (38.2)	0.3630
	little edema (1)	33 (68.7)	23 (47.9)	29 (53.2)	
	edema in 1/2 of nostrils (2)	3 (6.3)	10 (20.8)	4 (8.5)	
	edema in whole nostrils (3)	–	–	–	

**Kruskal–Wallis test for ordered contingency tables (multiple comparison)

Table 5. Outcome of symptoms and signs 3 days after treatment

Variables	Outcome+	Clemastine fumarate (N = 48) (%)	Chlorpheniramine maleate (N = 48) (%)	Placebo (N = 47) (%)	P value**
1. Nasal discharge					
–Frequency	worse	3 (6.2)	1 (2)	1 (2.1)	
	same	11 (23.0)	11 (23)	17 (36.2)	0.4996
	improved	34 (70.8)	36 (75)	29 (61.7)	
	p value*	0.0001	0.0000	0.0000	
–Character	worse	2 (4.1)	2 (4.1)	5 (10.5)	
	same	12 (25.0)	11 (23.0)	22 (46.8)	0.0143
	improved	35 (72.9)	35 (72.9)	20 (42.5)	
	p value*	0.0000	0.0000	0.0000	
	***	0.6448	0.0172		
		0.0085			
–Amount	worse	4 (8.3)	–	1 (2.1)	
	same	16 (33.3)	22 (45.8)	23 (48.9)	0.8377
	improved	28 (58.3)	25 (54.2)	22 (46.8)	
	p value*	0.0003	0.0000	0.0005	
2. Cough	worse	3 (6.2)	5 (10.4)	2 (4.2)	
	same	26 (54.2)	24 (50.0)	32 (68.1)	0.6877
	improved	19 (39.6)	19 (39.6)	13 (27.6)	
	p value*	0.002	0.0053	0.0214	
3. Swelling of nasal turbinate					
	worse	1 (2)	–	–	
	same	36 (75)	39 (81.2)	37 (78.7)	0.9531
	improved	11 (23)	9 (18.8)	10 (21.3)	
	p value*	0.0108	0.007	0.0051	

*Wilcoxon match paired rank sum test (paired data)
**Kruskal-Wallis test for ordered contingency tables (multiple comparison)
***Mann-Whitney with Bonferroni Correction
+Derived from (pretreatment score)-(post-treatment score) worse = -1 to -3, same = 0, improved = 1 to 3

Study Authors' Conclusions: The authors were convinced that viral nasopharyngitis is a self limited illness. There is no beneficial effect of treating the common cold with antihistamines when compared to placebo, except when the child has copious nasal discharge. Clemastine improved the character of nasal discharge significantly.

Comments:

- *It is not clear if the design of the study allowed for a true blinding. Although all medications were prepared in equal volume, the frequency of dosing of the two active treatment groups was still different; clemastine[11] was 2x/day because it is longer acting while chlorpheniramine was 3x/day.*
- *Cough is not an indication of either active treatment.*
- *The weight-based dosing of chlorpheniramine is not consistent with the monograph (see table A-1). The dosing should be of 1 mg every 4 to 6 hours (maximum of 6 mg in 24 hours) in children 2 to 6 y/o.[12] It is not clear if and how a dosing of 3x/day was defined for the parents, this can be interpreted as every 4, 6 or 8 hours.*
- *It is not clear if the symptom rating scale was defined or described to the parents.*

[11] Clemastine is a first generation antihistamine marketed in the U.S. as an OTC product for the relief of allergic rhinitis symptoms in adults and children 12 years and older in solid dosage form. The clemastine syrup formulation for use in children 6 to 12 y/o is available for prescription use only for the same indication. This drug was originally approved as a prescription drug through the NDA process and was switched OTC.

[12] Professional labeling.

- *Scoring for some of the symptoms may be confusing. For example, in scoring nasal discharge, differentiating "secretion in nostril" from "secretion from nostril" and "dry nostril" from "no secretion" may be confusing to the patient. Another is the character of nasal discharge, "white and thick (2)" and "clear (3)" should be reversed in order because the former should be considered worse than the latter.*
- *Once a day assessment of symptoms may not be adequate. The timing of evaluation of the effect of the test drug should occur when the efficacy of the drug is expected to occur; the study did not take into consideration that treatment effect may occur within an hour after treatment.*

7) Weipple G.
Therapeutic Approaches to the Common Cold in Children
Clinical Therapeutics 1984, Vol. 6 (4), 475-82.

Design and Methods: This was a randomized, double blind study to compare two cough syrup preparations (SCH 399 vs. expectorant syrup) in 60 children ≥ 4 y/o with cough and cold symptoms (common cold) 24 to 48 hours before enrollment. Patients were excluded if they had an underlying medical illness or T>99.9°F (37.7°C). Children received either SCH 399 or expectorant syrup:

- Each teaspoonful (5 ml) of SCH 399 syrup contained:
  1 mg azatadine maleate[13], 60mg pseudoephedrine sulfate, 20mg dextromethorphan HBr
- Each 100 gm of the expectorant syrup contained:
  0.205 gm diphenhydramine HCl, 2 gm ammonium Cl,
  1gm sodium citrate, 0.017gm menthol

Children received 2.5 ml of either preparation 3x/day (children 4 to 6 y/o) or 4x/day (children 6 to 12 y/o) for 5 days.[14]

At the initial visit, the degree of tiredness/drowsiness and achiness was evaluated, and the severity of sore throat was graded on a five-point scale ranging (0=absent to 4=severe). The following were all rated on a 4-point scale (0=none and 3=severe):

- Subjective symptoms: nasal congestion, rhinorrhea, sneezing, postnasal drip, lacrimation, headache and cough (0=none and 3=severe).
- Objective signs: nasal secretion, swelling and hyperemia of the nasopharyngeal mucosa, and obstruction of the left and right nostrils were all rated on a 4-point scale (0=none and 3=severe).

Included were patients who have the following ratings:

- at least a moderate degree of nasal congestion and/or rhinorrhea and cough (a rating of ≥2 on each symptom),
- subjective symptoms totaling at least 8 (except headache, aching, tiredness/drowsiness and sore throat)

[13] Azatadine maleate is an oral antihistamine discontinued in the United States.
[14] Manufacturer's recommended dose for the expectorant product is as follows: children 4 to 8 years of age, ½ teaspoonful 3-4x/day; children 8 to 14 years of age, one teaspoonful 3-4x/day.

- objective signs totaling at least 4
- sore throat rating ≤ 3.

Symptoms of tiredness/drowsiness and aching were not required for entry. The severity of signs and symptoms was recorded at initial (day 0), interim (day 3), and final (day 5) visits for overall response. The physician asked each patient at the interim visit when the improvement in symptoms was first observed. At the interim and final visits, overall therapeutic response was rated by the physician as: excellent (≥75% improvement) to poor (< 30% improvement) and exacerbation (worsening or flare) of signs and symptoms since initial visit.

Physician evaluation of overall therapeutic response, severity of individual signs and symptoms, and onset of relief were analyzed. To compare the severity of signs and symptoms, four scores were tallied for each patient:

- the sum of scores for the six subjective symptoms that constituted the initial symptom score of 8;
- the sum of scores for all ten subjective symptoms including tiredness/drowsiness, headache, sore throat pain, and achiness;
- the sum of scores for the 5 objective signs and
- the sum of total scores for the subjective symptoms and objective signs.

Results: A total of 56 patients completed the study and were evaluated for efficacy: SCH 399=29 and expectorant syrup=27. At days 3 and 5, patients treated with SCH 399 experienced a significantly greater degree of relief ($p < 0.001$) in 5 of 10 subjective symptoms (rhinorrhea, nasal congestion, postnasal drip, sneezing, lacrimation) and in all objective signs. Overall, the two treatment regimens were statistically comparable ($P > 0.10$) in relieving the subjective complaints of headache, achiness, drowsiness, cough, and sore-throat pain. Based on physician evaluations at interim and final visits, patients treated with SCH 399 showed a significantly better response to therapy ($P < 0.001$). More than 75% of the patients treated with SCH 399 demonstrated an excellent therapeutic response.

Adverse events: No adverse events were reported by patients or observed by the physician.

Study Author's Conclusion: Results demonstrate the superior efficacy of SCH 399 syrup in relieving symptoms of the common cold with associated cough. SCH 399 was safe and well tolerated when administered at a dosage of ½ teaspoonful 3 to 4x/day to children 4 to 11 y/o.

Comments:

- *This study lacks a placebo arm.*
- *It is stated that the study is double-blind. However, it was not clearly specified that the physician is blinded, this may effect efficacy assessment.*
- *The dose for pseudoephedrine was twice and dextromethorphan was 50% more than the recommended dose for children 4 to 6 y/o; the dose for children 6 to 12 y/o was consistent with the monograph for both drugs. However, the frequency of dosing for*

either drug was not consistent with the monograph dosing (see table A-1). The dosing of the comparator expectorant drug is unclear since it was expressed per 100 gm. It was not specified how dosing was determined; the dosing frequency for diphenhydramine (one of the ingredients in the expectorant syrup) was not consistent with the monograph.

- *A dosing frequency of 3 or 4x/day is non-specific and may not be adequate to elicit the effect of the drug.*
- *Headache, aching, tiredness/drowsiness or sore throat are symptoms that are unlikely to benefit from the tested drugs.*
- *It was not clear if symptom scoring at baseline was defined for the patients, and how signs and symptoms were measured. The degree of improvement in scores for each symptom was not provided in the study.*
- *It is not clear who scored the objective signs; it is assumed that patients scored the subjective symptoms although this was not specified. It is also not specified how data was collected.*
- *The rating of overall therapeutic response by the physician was not defined or explained.*
- *The time interval from initiation of therapy to the recording of the severity of signs and symptoms on days 3 and 5 seem to be too long. The timing of evaluation of the effect of the test drug should occur when the efficacy of the drug is expected to occur.*
- *The drug that claimed efficacy contained pseudoephedrine as an active ingredient while the other drug did had have pseudoephedrine.*
- *Azatadine maleate is an oral antihistamine that has been discontinued in the U.S.*
- *This study was conducted in Austria, although some of the active ingredients are included in the monograph list, neither combination product is approved in the U.S.*

8) Fisher, Peter.
Use of an antihistaminic drug for treatment of the common cold at a summer camp for boys.
American Medical Assn. 1951 Apr; 81(4):530-3.

The objective of the study was to determine if taking an antihistaminic medication will prevent or cure the common cold in its early stages.

Design and Methods: This was a placebo controlled, single-blind study conducted at a boys summer camp in Maine, participants were 260 boys, 9 to 16 y/o with early symptoms of cold. Forms were filled in for each boy coming to the dispensary for treatment of a cold. Patients were placed alternately in the two groups so that the selections were entirely at random. One group was given tripelennamine[15] (pyribenzamine®) hydrochloride, 50 mg 4x/day for boys ≥12 y/o and 25 mg 4x/day <12 y/o. The other group was given a white lactose tablet given 4x/day. No one but the author was aware of the true nature of the drug. All therapy was continued for 48 hours despite cessation of symptoms. If at the end of this time symptoms still persisted, routine symptomatic therapy was started. Patients were evaluated 4x/day; at the completion of therapy each boy was questioned about the

[15] Tripelennamine is discontinued in the U.S.

symptoms still present and the severity of these symptoms as compared with those at the start of therapy.

Results: There were 100 studies done for 88 boys, 12 patients having two courses of treatment. There were 26 records that were discarded: 17 due to incomplete therapy and 9 due to disease complications. For purposes of tabulation, each case was placed in one of four categories: cured, improved, no change and worse. The results in the two groups are almost identical.

Table 6: The Results of Early Treatment of Colds with Tripelennamine as Compared with a Control Medication

	Tripelennamine	Placebo
Patients studied	87	87
Cured	11	11
Improved	17	17
No change	5	6
Worse	4	3
Side reactions	4	5

Twelve patients received treatment with both drugs, hence, were their own controls. Of these 12 who received both forms of treatment, 5 reported better results with tripelennamine than with the placebo, 4 claimed better results with the placebo than with tripelennamine and 3 reported that the result was the same with both forms of therapy.

Adverse events: Four patients treated with tripelennamine complained of drowsiness, as did a similar number in the control group.

Study Author's Conclusion: Tripelennamine proved to be no more effective than a placebo in the treatment and prevention of the common cold in its early stages. It was evident in this study that giving of medication for the common cold, be it placebo or tripelennamine, gave satisfaction to the majority of patients.

Comments: The process of randomization in this study was not clear. This was a single-blind study. The patients were blinded but not the investigator. The number of patients in the study was small and it is not clear how dosing was determined. It is not clear if the categories for symptom assessment were explained to patients. The study states that there were 100 studies done for 88 boys; it is not clear why there were only 100 studies or evaluations if patients were evaluated 4x a day. Tripelennamine is an antihistamine that was approved by the FDA in 1946 and has been discontinued in the U.S.[16]*; it appears to be available in other countries.*

[16] Clinical Pharmacology Online (http://cpip.gsm.com/) accessed 7-30-07.

The following three studies in children were referenced in evaluating the effectiveness of some active ingredients found in cough and cold drug products listed in the monograph:[17]

9) Reece CA, Cherry AA, Reece TA, et. al.
Tape Recorder for Evaluation of Coughs in Children, Evaluation of Antitussive Agents
Amer J Dis Child, Aug 1966, Vol 112 (2), 124-8.
**This study was used to evaluate the effectiveness of dextromethorphan in children in the monograph.*

The objective of this study was to determine whether two antitussive preparations would suppress spontaneous cough in children and whether the duration of effect of a single dose was sufficiently long to relieve the cough throughout the sleeping hours.

Design and Methods: The study design was twofold: inpatients hospitalized for respiratory illness and ambulatory patients. Inpatients: a total of 65 children (2 months to 12 y/o) were selected at random from inpatients hospitalized for respiratory illness and were evaluated objectively by means of a tape recorder. Ambulatory: patients were in private practice[18] and evaluation was by observations of the mother. The following were the treatment used:

- Medication A: Triaminicol syrup, each 5 ml contains: phenypropanolamine (PPA)[19] 12.5 mg, pheniramine maleate 6.25 mg, pyrilamine maleate 6.25 mg, dextromethorphan HBr 15 mg, ammonium chloride 90 mg.
- Medication B: Dorcol Pediatric Cough syrup, each 5 ml contains: dextromethorphan Hbr 7.5 mg PPA HCl 8.75 mg, glyceryl guiacolate 37.5 mg, alcohol 5%.
- Medication C: Placebo syrup (resembles medication B in color and taste).

Table 7: Amounts Medications A , B, and C Administered to Equalize the Dextromethorphan Content

Age of Children	Medication A	Medication B	Medication C
Less than 2 years	1.25 ml	2.5 ml	2.5 ml
2 to 6 years	2.5 ml	5.0 ml	5.0 ml
7 to 12 years	5.0 ml	10.0 ml	10.0 ml

A: Triaminicol syrup, B: Dorcol Pediatric Cough syrup, C: Placebo syrup

Inpatient Study: A total of 22 patients, 2 months to 9 y/o, were selected. Included were children with cough hospitalized due to acute respiratory infection (e.g. bronchitis, pneumonia, asthma). The testing period required 3 days. The child was not informed that a study was in progress, nor was he told that cough medicine would be given. Recordings were made for an 8-hour interval during the night. Antitussive medication was withheld during the first day and baseline recordings of cough were made between 10 PM and

[17] Advance Notice of Proposed Rule (ANPR) 41FR p.38312, 9-9-76.
[18] From the inpatient pediatric service of the University of Kansas Medical Center and from the ambulatory private practice of one of the authors.
[19] PPA is a decongestant that is no longer marketed in the U.S.

6 AM. After an initial 24-hour control period, medication A, B, or C was given orally by teaspoon every 8 hours, for a total of 5 doses. The individual dose was calculated according to standard age-weight pediatric dose recommendations and was based on the milligram content of dextromethorphan as the active ingredient to be tested.

Ambulatory Study: There were 43 children, aged 2 months to 12 years with a chief complaint of cough who participated in the study. None had chronic illness of the respiratory system. After being examined, one of the medications (A, B, or C) was presented to the mother with instructions to give it to the child and to report its effect as a cough medicine, its duration of action in stopping the cough or reducing the frequency of cough and whether or not the child accepted or rejected the medication because of color, taste, or other factors. The final report was recorded on a standard form.

Results:

Inpatient study: Results were obtained from 22 children (A=7, B=8, C=7). The total 8-hour cough count, and the cough count at hours 6 to 8 were averaged for the 3 days, and the percentage change from control values was calculated. Both of the antitussive syrups containing dextromethorphan were more effective than the placebo in suppressing cough. The authors stated that the superiority of the antitussive medications over the placebo was so obvious that no statistical analysis was required. The cough count between the 6 to 8 hour period following the bedtime dose was reduced 60% to 65% from the baseline level compared to 11% with placebo. A high frequency of night coughs was observed in two the children with 401 (50/hr) and 591 (74/hr) coughs in an 8-hour interval.

Table 8: Results of the 2-Hr Increment Cough Count and the Total Cough Count During the 8-Hr Night Recording: Comparison of Control Period With Period After 5 Doses of Medication (Inpatient Study)

		Cough Count, 1st Day (Baseline)					Cough Count, 3rd Day (After 5 doses medication)				
		Hourly Increments					Hourly Increments				
Patient No.	Medication	0-2	2-4	4-6	6-8	Total	0-2	2-4	4-6	6-8	Total
1	A	0	0	0	1	1	0	2	8	3	13
2		34	14	42	88	178	1	0	0	1	2
3		0	96	9	45	150	20	14	11	27	72
4		87	4	4	2	97	4	13	24	2	43
5		1	1	0	3	5	1	0	4	1	6
6		16	0	2	1	19	18	4	10	2	34
7		34	65	59	36	194	46	48	41	35	170
				Total		644			Total		340
8	B	0	4	0	1	5	0	9	6	1	16
9		25	37	4	48	114	10	2	0	20	32
10		36	11	29	36	112	75	23	123	21	242
11		59	20	47	74	200	5	6	38	9	58
12		5	3	3	0	11	0	2	5	0	7
13		144	166	106	175	591	134	51	66	63	314
14		20	5	3	18	46	43	17	0	2	62
15		66	46	22	19	153	6	33	0	12	51
				Total		1,232			Total		782
16	C	—	—	—	11	11	34	2	16	5	57
17		2	150	0	0	152	28	0	15	35	78
18		26	17	20	12	75	0	31	49	22	102
19		6	0	0	0	6	31	6	5	7	49
20		18	2	70	0	90	5	4	12	9	30
21		129	23	28	221	401	124	196	70	140	530
22		4	3	2	0	9	5	2	1	0	8
				Total		744			Total		854

Table 9. Total 8-Hr Cough Count and the Cough Count at Hours 6 to 8 Averaged for the Third Day, With Percentage from Control Values (Inpatient Study)

	Medication A	Medication B	Medication C
Average baseline, total 8-hour cough count	92	154	106
Average baseline, 6-8 hour cough count	25	46	35
Average third day, total 8-hour cough count	49	97	122
Average third day, 6-8 hour cough count	10	16	31
Total 8-hour cough, depression (3rd day vs baseline counts)	47 % decrease	37 % decrease	15 % increase
Cough depression, 6-8 hour (3rd day vs baseline counts)	60 % decrease	65 % decrease	11 % decrease

Medication A: Triaminicol, Medication B: Dorcol, Medication C: Placebo

Ambulatory Study: Results were obtained from 43 children (A=16, B=13, C=14). The antitussive response to all three products was relatively satisfactory. Between the sixth and ninth hours after administration, the cough suppressant effect of the two antitussive syrups containing dextromethorphan was 46% to 56%, compared to only 21% in the placebo group.

Table 10: Antitussive Response of the 3 Syrups Given to Ambulatory Patients

	Medication		
	A	B	C
Number of patients studied	16	13	14
Duration of antitussive action by 3-hr increments	%	%	%
6 to 9 hours	56	46	21
3 to 6 hours	19	23	43
0 to 3 hours	0	8	0
Incomplete report	25	23	36
Antitussive response	%	%	%
Satisfactory	69	69	57
Unsatisfactory	25	23	29
Incomplete report	6	8	14

Medication A: Triaminicol, Medication B: Dorcol Pediatric, Medication C: Placebo

Adverse events: There were no adverse effects reported in the study.

Study Authors' Conclusion: Inpatient and ambulatory studies were mutually confirmatory, showing that both antitussive syrups containing dextromethorphan, when given in the doses used at 8-hr intervals, provide an antitussive effect for up to 8 hours.

Comments:

- *The dose and dosing frequency for dextromethorphan were consistent with the monograph.*
- *The endpoint measured was cough for 8-hours overnight for inpatients, this was appropriate for the symptom being evaluated. The use of a tape recorder was an objective and preferable measure of cough counting.*
- *The 8-hour recording of cough episodes also captured the expected duration of effect of the drug (which is 8 hours for dextromethorphan depending on the dose).*
- *Cough counts at baseline and at the end of the treatment period were provided which was useful information.*
- *The randomization process is not clear as well as the blinding; it is not clear if the investigators were blinded or not.*

- *The patients who participated in the inpatient portion of the study had underlying significant medical illnesses, which were most likely treated with other medications such as antibiotics, bronchodilators, steroids, etc. depending on their diagnosis. Thus, a patient's underlying illness (which was not specified for each patient) and/or concomitantly administered medications may have contributed to the effect of the tested drugs.*
- *For the ambulatory portion of the study, the frequency and duration of treatment was not clearly specified.*
- *In the ambulatory study, patients were assessed by 3-hour increment over a 9-hour period to assess the duration of antitussive action. This frequent assessment of symptoms was very useful in evaluating the effects of the drug; however, 25 to 36% had incomplete report.*
- *In the ambulatory study, no baseline values were provided and it is not clear if symptom measurement was explained to the parents. The dosing frequency was also not specified.*
- *The number of patients in each treatment arm is too small in both the inpatient (n=7 to 8) and outpatient (n=13 to 16) portions of the study.*
- *The test medications were combination products, it is not clear to which of the active ingredients the effect of the medication could be attributed to. Both combination products contained PPA which is no longer marketed in the U.S.*
- *OTC medications that contain alcohol indicated for children are no longer marketed in the U.S.*
- *This study was used to evaluate the effectiveness of dextromethorphan in children in the monograph.*

10) McGovern JP, McElhenney TR, Hall TR, et. al.
Evaluation of effectiveness, dosage and toxicity of para-bromdylamine maleate (PM)[20] in allergic rhinitis of infants and children.
Annals of Allergy, Nov-Dec 1959; 17, 915-22
Although the indication of this study is not the common cold, it was referenced in the Panel Report in evaluating the effectiveness of brompheniramine in children.[21]

The objectives of the study were to determine the effectiveness, minimal dose by body weight, tolerance and toxicity of an antihistamine from the monoamine group for symptomatic relief of allergic nasal symptoms in the pediatric age group.

Design and Methods: This was a study in 485 infants and children with various allergic manifestations; 200 patients with perennial allergic rhinitis were selected by alternate allocation at the start of Dimetane® (parabromdylamine maleate) therapy for careful follow-up studies. Patients were divided into 3 groups: *infancy*-2 months to 2 y/o, *pre-school age*-2 to 6 y/o, *school age*-6 to 14 y/o. Each patient/parent was questioned repeatedly for any changes in allergic symptoms throughout the period of the study and observed at 1 to 2 week intervals. Dimetane® was given as an elixir (2mg/5cc) for

[20] Same as brompheniramine.
[21] Advance Notice of Proposed Rule (ANPR) 41FR p.38383, 9/9/76.

18 months. Results with respect to nasal symptoms were grouped as good, fair, or poor. These observations were made and graded independently by two observers. Results with respect to nasal symptoms were grouped as:

- Good: complete or highly significant relief, no signs of toxicity to the drug.
- Fair: some significant improvement, no signs of toxicity.
- Poor: minimal or no improvement or if with undesirable side effects.

Results: The minimal and usually effective dose of Dimetane® in *infancy* (n=73) was found to be 0.2 mg/lb/24 hours (0.44/kg/24 hrs.) given in 3 divided doses. With many infants, it was necessary to increase the dose to 0.5 mg/lb/24 hours (1.1 mg/kg/24 hours) before beneficial effects were noted. Good responses for nasal symptoms were obtained in 55, fair in 13, and poor to no benefit in 5 patients. The minimal and usually effective dose for nasal symptoms in the *preschool* age group (n=70) was 0.2 mg/lb/24 hrs (frequency not specified). Good response was obtained in 51, fair response in 14 and poor in 5. Fewer of these patients required larger amounts of the drug, 3 patients were noted to have mild drowsiness although not severe enough to require diminution or discontinuance of the drug. The minimal and usually effective dose required for beneficial results of perennial allergic rhinitis in the *school age* group (n=57) was 0.15mg/lb/24hrs. (frequency not specified). Out of 57 patients, good response was achieved in 43, fair in 13, and poor in 1.

Adverse Events: A two year old boy accidentally drank 5 oz. of Dimetane® elixir (60 mg or 2 mg/lb) with no apparent side effects. Another 4 y/o boy accidentally took 8 oz of Dimetane (96 mg or 2.5 mg/lb) and had mild, transient drowsiness. There were no undesirable side effects noted. Mild drowsiness was reported in 3 patients.

Study Author's Conclusions: Parabromdylamine maleate is a safe, effective antihistaminic agent with a very low incidence of undesirable side effects in infants and children. The average minimal effective dose for all ages was 0.2 mg/lb/24 hrs (0.44/kg/24 hrs). In infants, larger doses, even up to 0.5 mg/lb/24 hrs (1.1 mg/kg/24 hrs), often were required before maximum benefit was obtained. In 3 cases of marked over-ingestion, no symptoms suggesting CNS stimulation or other toxic symptoms were noted, such as those which have been described with other antihistaminic agents. No symptoms suggesting clinical bromism (PM contains a bromide molecule) were noted in 3 cases of over-ingestion or in those patients who had been receiving the drug daily for as long as 14 months.

Comments:

- *This study was referenced in the Panel Report in evaluating the effectiveness of brompheniramine in children although the indication studied was allergic nasal symptoms and not the common cold.*
- *This study had no placebo arm and therefore interpretation of data is limited.*
- *It was assumed that the study drug is efficacious and the objective was to determine the lowest effective dose and toxicity of the drug.*
- *It is unclear how initial dosing was determined and how dose was titrated. The usual dosing frequency for antihistamines is every 4 hours, not 3x/day.*
- *There was no mention of blinding nor randomization; therefore, there is a high likelihood of bias from both parents and observers.*

- *Improvement was based on overall improvement of nasal symptoms and not based on improvement of specific symptoms.*
- *The article states that "observations were made and graded independently by two observers"; it is not clear who and how patients were evaluated for their symptoms.*
- *The duration of the study is 18 months with symptom evaluation every 1 to 2 weeks interval, this interval between evaluation of symptoms was too long. It was not described how data was collected.*
- *Note that this study was conducted almost 50 years ago (1959).*

11) Lipschutz, Arthur.

Oral decongestant therapy in allergic respiratory diseases of children.

Annals of Allergy 1960, Sept vol 18:998 -1003.

This study was referenced to evaluate the effectiveness of pseudoephedrine in the monograph.

The objectives of the article were to discuss the oral use of sympathomimetic drugs in the therapy of allergic respiratory disease in children and to present the results of a double-blind study with one of the sympathoamines, d-pseudoephedrine.

Design and Methods: This was a double-blind study in a total of 200 children 4 months to 17 years old with respiratory disorders with or without associated allergies. A total of 148 children had an initial diagnosis of non-allergic respiratory disease categorized as pharyngitis, coryza, URI, tracheobronchitis, sinusitis and pneumonitis; 52 children had nasal allergy (seasonal and non-seasonal), bronchial asthma, asthmatic bronchitis and atopic dermatitis associated allergic rhinitis. Patients received one of the following treatments 4x/day for 3 days (dose not specified): triprolidine combined with pseudoephedrine, pseudoephedrine or placebo. No other drug therapy was employed. The drug response of the patients was judged as: *excellent*- relief was complete or virtually so, *good*- relief was obvious but only partial, and *poor*- little or no relief resulted.

Results: There were 22/25 (88%) patients with allergic respiratory disease who responded to pseudoephedrine combined with triprolidine, while 33/49 (67%) patients of non-allergic respiratory disease responded favorably. There were 15/17 (88%) patients who showed response to pseudoephedrine alone, while 44/65 (68%) of non-allergic children gave satisfactory results. There were 4/10 (40%) patients with allergic respiratory disease who responded to placebo and 19/34 (56%) of non-allergic respiratory disease responded to placebo. See table below:

Table 11: Results of Therapy in allergic vs. non-allergic patients

	Symptomatic Relief	Pseudoephedrine with Triprolidine	Pseudoephedrine	Placebo
Allergic respiratory diseases	Excellent	20% (5)	24% (4)	0% (0)
	Good	68% (17)	65% (11)	40% (4)
	Poor	12% (3)	11% (2)	60% (6)
Total		(25)	(17)	(10)
Non-allergic respiratory diseases	Excellent	16% (8)	14% (9)	21% (7)
	Good	51% (25)	54% (35)	35% (12)
	Poor	33% (16)	32% (21)	44% (15)
Total		(49)	(65)	(34)

Adverse Events: All patients took medications without any ill effects and no abnormal urinary or hematologic findings were observed. There were no untoward effects in the use of these drugs.

Study Author's Conclusion: Pseudoephedrine alone and triprolidine with pseudoephedrine are effective decongestant drugs when used in respiratory allergic and non-allergic diseases of children. They also stated that allergic rhinitis responds to oral sympathomimetics without the local rebound phenomenon or chronic stuffy nose frequently caused by topical sympathomimetic drugs.

Comments:

- *The dose given to patients was not specified in the study; the frequency of dosing was stated as 4x/day which was non-specific.*
- *There was no mention of randomization; there was also no specific endpoint identified.*
- *Improvement was based on overall response to the drug, there were no specific symptoms measured.*
- *It is not clear who evaluated the patient's response, the mother, the investigator, or both.*
- *It was not specified how, when and how often data was collected.*
- *Baseline values were not provided although the patients were their own controls.*
- *Participants had either allergic or non-allergic respiratory diseases. The methodology stated that there were no other therapies used, however, patients with tonsillitis, pneumonia, sinusitis and other respiratory infections treatable with antibiotics were included. It is not clear if these patients were treated with antibiotics.*
- *There was also no statistical analysis involved in this study; results were based on proportion of patients having symptomatic relief.*
- *The authors concluded that allergic rhinitis responds to oral sympathomimetics without the local rebound phenomenon; however, the study was conducted for 3 days only, which may not be long enough to evaluate for this rebound phenomenon.*
- *It appears from the result of this study that there may be a numerical trend favoring products containing pseudoephedrine.*
- *The number of patients in each treatment arm was very small especially the placebo group (n=10) in those with allergic respiratory diseases to make a generalized conclusion.*
- *This was an old study conducted at least 40 years ago and therefore was done under a different standard.*
- *This study was referenced to support the effectiveness of pseudoephedrine as a nasal decongestant in children in the monograph.*

B. Case Reports/Series

1) Gunn VL, Taha SH, Liebelt EL, and Serwint JR.
Toxicity of Over-the-Counter Cough and Cold Medications

Pediatrics 2001;108(3). URL: http://www.pediatrics.org/cgi/content/full/108/3/e52

This article presented 3 cases children in whom the authors believed suffered significant morbidity from OTC cough and cold preparations, requiring admission and treatment in a tertiary care hospital during a 13-month period:

- A 36-month old boy presents to the emergency department (ED) with lethargy, vomiting, bradycardia, tachypnea, and hypertension. The child's mother had given him an unspecified amount of Dimetapp® cold syrup containing phenypropanolamine (PPA) 12.5mg/5mL and brompheniramine 2mg/5mL several hours earlier. Past medical history was remarkable for prematurity and hydrocephalus with ventriculo-peritoneal (VP) shunt as a result of child abuse; his neurosurgeon determined without tapping his shunt - that shunt malfunction was not the source of the child's altered mental status. He was given intravenous fluids. Urine toxicology testing: positive for brompheniramine, other labs-normal. Diagnosis was mental status change secondary to antihistamine and sympathomimetic ingestion.

- A 35-month old boy was seen at the ED with a fever of 104°F, WBC=8.4, 33% bands, chest x-ray (CXR) showed left lobe infiltrate and cardiomegaly, a blood culture was sent. He was treated with IM ceftriaxone and discharged from the hospital, to follow-up with his pediatrician the next day. At the pediatrician's office, parents reported intermittent fever for 3 weeks, along with cough and rhinorrhea, and was being given only Children's Tylenol as instructed for fever. He had tachycardia[22] (150/min), T=99.1°F axillary; and appeared tired. CXR was repeated, no infiltrate; cardiomegaly persisted. An echocardiogram revealed a mildly dilated left ventricle and moderate left ventricular dysfunction, he was admitted to the hospital and scheduled for cardiac catheterization. Parents produced a bottle of Children's Tylenol Cold which they had been using for fever. It contained: acetaminophen (160mg/5mL), chlorpheniramine (1mg/5mL), dextromethorphan (5mg/5mL), and pseudoephedrine (15mg/5mL). His urine toxicology screen revealed 2 metabolites of chlorpheniramine. He was discharged improved on hospital day 3, tachycardia resolved and echocardiogram was within normal range 2 weeks after discharge.

- A 9-month old boy was sent to the ED due to persistent crying and fever 102°F for 6 days, cough for several weeks, emesis 3x/day, no diarrhea; and no sleep for 3 nights. He had cough for several weeks; fuzzy and nonconsolable the past week. His mother reported only giving him ¾ dropper of Motrin. On examination, he was screaming with a T=103.1°F, tachycardic (208 pm), BP=121/78 mmHg. CBC & CSF were normal. Several hours later, the infant was noted to be alert, active, and playful, and tolerating oral liquids. IM ceftriaxone was given and discharged from the hospital with

[22] The normal heart rate for a child 1 to 3 y/o is 90 to 150 bpm. The Harriet Lane Handbook, 17th ed.

instructions to return to the ED the following day for reevaluation. Twelve hours later, he came back in cardiopulmonary arrest and died.

Autopsy was grossly normal. Postmortem blood analysis from the heart revealed markedly elevated levels of several substances: pseudoephedrine = 10 mg/L, PPA = 1.4 mg/L, and dextromethorphan = 0.6 mg/L. Postmortem liver analysis showed a concentration of pseudoephedrine of 14 mg/L and PPA of 0.5 mg/L. Additional investigation revealed numerous doses of OTC cough and cold preparations had been given to the infant. The cause of death was mixed drug intoxication, unintentional.

The following therapeutic concentrations were discussed in the article:

- PPA: therapeutic concentrations in males have been reported to be 0.11 to 0.40 mg/L.
  - Fatal cases been reported with postmortem blood concentrations of 2 mg/L to 4.6 mg/L.
- Dextromethorphan: therapeutic drug concentrations vary widely and have been reported to average from 2.4 μg/L to 207 μg/L (0.002 mg/L to 0.207 mg/L).
  - Two fatalities in adults reported concentrations of 3.3 to 9.2 μg/L in blood.
- Pseudoephedrine: A therapeutic drug concentration is reported to be 0.21 to 0.77 mg/L.
  - A 2-year-old child who ingested a large amount of pseudoephedrine tablets had a postmortem blood level of 66 mg/L.
  - Another fatal overdosage had a concentration of 19 mg/L in the blood and 33 mg/L in the liver.

Authors Conclusion: Three cases of children experiencing significant adverse effects and toxicity from OTC cough and cold preparations are presented. Health care providers have the opportunity to intervene by inquiring specifically about OTC cough and cold medication use, and by educating parents on the lack of demonstrated benefit and known risks in the pediatric population-- as recommended by the AAP.

Comments: In all cases, it is not clear how much of the cough and cold medicines were administered to patients and if all were given more than the recommended amount. The authors believed that although the presence of the antihistamines in the urine toxicology test in two cases does not establish causality, the symptoms and their resolution correlate with adverse effects from the drugs and timing of their metabolism. Therapeutic and toxicity data on serum and postmortem drug concentrations of these cough medications in children is limited and therefore difficult to interpret. An underlying infection was a confounding factor in the second and third cases which could have partially or totally explained the patients' symptoms. It is not clear from these cases what and how much of the active ingredients in the cold medicines contributed to the child's symptoms. The potential for confusion on the appropriate dosing in infants and children with pediatric formulations of OTC cold medications is a possibility in some or all of the cases.

In the first case, it was not stated why the child was given such medication since there was no mention of cold symptoms. Lethargy, one of the symptoms manifested by the patient in this case is a known CNS side effect that can occur during therapy with brompheniramine. Similar to other sympathomimetics, PPA can cause hypertension during therapy (PPA has been pulled

out of the market due to its association with hemorrhagic strokes). Bradycardia and tachypnea are not known to be reported side effects for either drug.

In the second case, the authors hypothesize that the patient developed left ventricular dysfunction because of sustained tachycardia from the ingested sympathomimetic and antihistamine agents. Cardiovascular adverse effects from sympathomimetic drugs generally occur at excessive dosage or in patients at higher risk (patients with cardiac disease)[23]. For antihistamines, the most frequent adverse effect is sedation; in acute poisoning, symptoms are related to their central excitatory effects.[24] It was not specified how much and how many total number of days the cough and cold medicines were administered to the patient. The parents thought that they were administering a product with an antipyretic only (single-ingredient) but turned out to be a combination of 4 active ingredients. Therefore, this was a clear case where a caregiver unintentionally administered the wrong cough and cold preparation for 3 weeks in a patient with an underlying systemic infection.

In the third case, it appears that the mother had been administering numerous doses of OTC cough and cold preparations to the infant on her own without the supervision of a physician. The postmortem blood analysis from the heart revealed a level of pseudoephedrine 10 mg/L, this is at least 20x higher than expected (0.18 mg/L to 0.50 mg/L).[25] Dextromethorphan was 0.6 mg/L (expected level=0.0024 mg/L to 0.207 mg/L) [26] and PPA was 1.4 mg/L (expected level= 0.11 to 0.40 mg/L), these were 3x higher than the reported therapeutic levels in adults. Although therapeutic and toxicity data on serum and postmortem drug concentrations of these cough medications in children is limited, it is obvious that the child received an excessive amount of pseudoephedrine. It is likely that the child received excessive amount of cough and cold medications, specifically pseudoephedrine, because the parents were not aware that they are simultaneously administering cold preparations that have the similar active ingredients in a patient with an underlying infection. Medication error leading to overdose likely contributed to the patient's death.

2) **Marinetti L, Lehman L, Casto B, et. al.**
Over-the-Counter Cold Medications-Postmortem Findings in Infants and the Relationship to Cause of Death
Journal of Analytical Toxicology, Vol. 29, October 2005

The Montgomery County (Ohio) Coroner's Office has encountered a series of 10 infant deaths (<12 months old) over an 8-month period with toxicology findings that include a variety of drugs commonly found in over-the-counter (OTC)[27] cold medications. A common history in the cases was that an infant was given OTC cold medication. The majority of these deaths were reported to be either toxicity from the OTC cold medications directly or as a contributory factor in the cause of death. The toxicology findings in the blood of these

[23] Clinical Pharmacology online (http://cpip.gsm.com/) accessed 8-17-07.
[24] Ibid.
[25] From a PK studies of pseudoephedrine in children 6 to 12 y/o with seasonal allergic rhinitis (Simons FE, et al. 1996) and children 2 to 12 y/o after therapeutic doses (FDA, unpublished data).
[26] Boland et al. Journal of Analytical Toxicology, Vol. 27, October 2003.
[27] The drugs detected were ephedrine, pseudoephedrine, dextromethorphan, diphenhydramine, chlorpheniramine, brompheniramine, ethanol, carbinoxamine, levorphanol, acetaminophen, and the anti-emetic metoclopramide.

10 cases are tabulated below.

Case 1*: A 12-month old infant with Down's Syndrome dependent on a feeding tube had recent fever and upper respiratory tract congestion. A few days prior to death, the infant was treated with Children's Tylenol Plus-Cold and Cough. The cause of death was determined to be Klebsiella pneumoniae sepsis with toxic levels of Childrens's Tylenol Plus-Cold and Cough contributing. Electrolytes: Na=164 meq/L, Cl=149 meq/L, and urea nitrogen=91 mg/dL concentrations showed evidence of dehydration.

Case 2: An 8-month old infant had reported fever and congestion, mother was advised to give administer infant Tylenol and a cool bath; 12 hours later, he was found face-down and unresponsive in the crib. The scene investigation revealed a 4-ounce bottle of Childrens Tylenol Plus-Cold and Cough cherry flavor on the kitchen counter with approximately ½ ounce remaining. There was also a large soft pillow and multiple blankets in close proximity to where the infant was found in the crib. The cause of death was positional asphyxia with multiple drug intoxication contributing.

Case 3*: A 4-month old infant was found unresponsive in an unknown position, only blood and bile specimens were submitted; there was insufficient specimen submitted for toxicological analyses. The autopsy results are unknown, and the cause of death is unknown.

Case 4*: A 1-month old infant with cleft palate exhibited cold-like symptoms for 3 days prior to death. Infant was seen by a pediatrician, and Dimetapp® was purchased by the parents and administered for congestion. Two days later, the infant was fed at 1 a.m. After this feeding, the infant refused formula. The infant was placed in a bouncer in a reclined position at 19:00 hours. At 20:15 hours, the infant was found unresponsive. Cardiopulmonary resuscitation was given without success; the infant was pronounced dead at 21:01 hours. The autopsy findings showed meningitis due to Streptococcus pneumoniae with otitis media and bronchopneumonia, cardiomegaly and brompheniramine intoxication. The approximate therapeutic range for brompheniramine in an adult is 0.005–0.02 mg/L, this infant's brompheniramine level was 0.04 mg/L.

Case 5*: A healthy 2-month old infant had cold like symptoms for two days later. The infant was placed on her belly for a nap, 2 hours later, the infant was unresponsive. The parents transported the infant to the hospital. The infant and was pronounced dead upon arrival. Autopsy findings were unremarkable. The cause of death was determined to be acute intoxication with dextromethorphan, ephedrine, pseudoephedrine, and carbinoxamine. (There were no details on the medications used in this report).

Case 6: A 3-month old infant history was remarkable for possible overlay[28] followed by increasing lethargy. The child was diagnosed with non-accidental brain injury. The autopsy findings included bilateral florid conjunctival petechiae, bilateral periocular florid petechiae, a small subdural hematoma of the left cerebral hemisphere, with evidence of an older hemorrhage. There was also a scalp contusion, cerebral edema, and diffuse bilateral retinal

[28] Overlay: to cause the death of by lying upon. Merriam-Webster Dictionary Online (http://www.m-w.com/medical/overlay) accessed 8-10-07.

hemorrhages. The infant also had a healing right tibia fracture. The heart blood was positive for diphenhydramine. The cause of death was determined to be compressional asphyxia.

Case 7*: A 1½- month old infant died due to compressional asphyxia due to overlay. According to the nurse at the hospital, the mother contacted her and said that the infant had a cold for the past four or five days and was given three doses of Tylenol. Siblings ages 3, 6 and 9 had been diagnosed with echovirus. The pathologist felt that the drugs did not play a significant role in this death.

Case 8*: A 3-month old infant was found dead in bed co-sleeping with its mother in a women's shelter. The infant had coldlike symptoms recently and was medicated with Infant Tylenol and OTC cold remedies. The autopsy results included multiple petecchia on the lungs but none on the heart. The infant's doctor suspected intoxication by overdose with OTC cold medications; however, the coroner ruled the cause of death to be Sudden Infant Death Syndrome.

Case 9*: A 3-month old premature infant was fed and placed on the stomach in a crib, 3 hours later, was found unresponsive. The infant's death occurred within 12 hours of receiving immunizations. The parents gave two doses of Tylenol Cough and Cold pediatric formulation (0.6 mL) to ease possible fever or pain from the immunizations. History was remarkable for congestion and a viral infection approximately one month prior to death. Infant was evaluated for a possible allergic reaction to the recent immunizations; both tryptase and IgE came back within normal limits. The autopsy results and cause of death are unknown. The femoral blood was positive for ephedrine, pseudoephedrine, dextromethorphan and acetaminophen.

Case 10*: A 5-month old infant had a history of ear infections and congestion. An antibiotic was prescribed, an OTC cold medication containing dextromethorphan was also given (not stated if given upon the physician's advice). The infant was placed on his stomach for a nap at about 09:30 hours. At 12:15 hours, the mother found the infant unresponsive, and EMS pronounced the infant dead at 12:22 hours. The residence was clean, and the crib was free of clutter and extra blankets. The dose and the exact OTC product were not known. The cause of death was acute multiple drug intoxication. The investigation of this death led to the discovery that the infant's 3- and 4-year old siblings were routinely given OTC cold medications to sedate them; the children have been removed from the home. Dextromethorphan was found in the blood and urine collected from the siblings.

The following table lists the toxicology findings in the blood of the above 10 cases:

Table 12: Toxicology Findings in the Blood for All 10 Cases

Table II. Toxicology Findings in Blood for all 10 Cases

Case/Site	Age (months)/ Gender	Ephed (mg/L)	Pseudo (mg/L)	Bromphe (mg/L)	Chlorph (mg/L)	Dextro (mg/L)	Diphe (mg/L)	Apap (mg/L)	EtOH (g%)	Carbin (mg/L)	Metocl (mg/L)	Levorp (mg/L)
1*/CB†	12/M	0.39	1.5	ND	ND	0.55	ND	117	0.02	ND	ND	ND
2/PB	8/M	0.14	1.1	ND	0.08	0.37	ND	6.6	ND	ND	ND	ND
3*/HB	4/M	0.12	0.67	INS	INS	INS	INS	INS	ND	INS	INS	INS
4*/PB	1/F	< 0.05	0.27	0.04	ND	ND	ND	ND	ND	ND	ND	ND
5*/HB	2/F	0.50	2.2	ND	ND	0.04	ND	16	ND	0.08	ND	ND
6/HB	3/F	ND	ND	ND	ND	ND	0.14	ND	ND	ND	ND	ND
7*/HB	1.5/M	0.06	0.50	ND	ND	ND	ND	3.4	ND	ND	ND	ND
8*/HB	3/M	0.09	2.9	ND	ND	0.03	ND	24	ND	ND	ND	0.04
9*/FB	3/F	0.04	0.52	ND	ND	0.04	ND	1.7	ND	ND	ND	ND
10*/CB	5/M	< 0.10	1.4	ND	ND	0.09	ND	6	ND	0.07	0.67	ND

* Not Montgomery County cases.
† Abbreviations: CB, cavity blood; PB, peripheral blood; HB, heart blood; FB, femoral blood; M, male; F, female; ND, not detected; and INS, insufficient specimen for complete analysis.

Authors' Conclusions: By documenting cases such as the 10 presented here, data regarding concentrations of OTC medications can be correlated with case histories and causes of death to expand the database and to aid in the interpretation of toxicology findings. In addition, the profession of forensic toxicology can help validate the dangers of misuse of OTC cold medications in infants. This practice can result in toxicity leading or contributing to the death of the infant.

Comments: There is limited clinical information on the therapeutic and toxicity data on serum and postmortem drug concentrations of OTC cough and cold medications in children. The following are the reported therapeutic blood concentrations for some of the OTC cough and cold medications:

- *Pseudoephedrine: 180 to 500 ng/mL* ***(0.18 mg/L to 0.50 mg/L)*** *in children 2 to 12 years old.* [29]
- *Brompheniramine:* ***0.018 mg/L to 0.022 mg/L*** *in adults (2 mg orally every 4 h for 7 days) in adults.*[30]
- *Chlorpheniramine:* ***10 µg/L*** *in adults (2 mg q 4 hours x 3 doses)*[31].
- *Dextromethorphan:* ***0.0024 mg/L to 0.207 mg/L*** *in adults (30 mg orally every 4 h for 7 days).*[32]
- *Diphenhydramine****: 0.066 mg/L to 0.083 mg/L*** *in adults (50 mg oral dose in adults).*[33]

[29] From a PK studies of pseudoephedrine in children 6 to 12 y/o with seasonal allergic rhinitis (Simons FE, et al. 1996) and children 2 to 12 y/o after therapeutic doses (FDA, unpublished data).
[30] Boland et al. Journal of Analytical Toxicology, Vol. 27, October 2003.
[31] Baselt, Randall C. Disposition of toxic drugs and chemicals in man. 7th ed. p 214-5.
[32] Ibid.
[33] Baselt, Randall C. Disposition of toxic drugs and chemicals in man. 7th ed. p 362-3.

- *Guaifenesin:* ***1.4 mg/L*** *in adults (single 600 mg oral dose).*[34]
- *APAP: 10-30 µg/mL*[35] ***(10-30 mg/L)****.*

From the limited clinical information provided, the presence of one or more of the active ingredients found in cough and cold medications including acetaminophen in the toxicology findings in the blood is common in all 10 cases. Although in some of the cases, parents do not report giving these medications to the child, these were detected in the patient's blood. Some of the patients had postmortem blood levels that were at least double the known therapeutic blood concentrations for some of the OTC cough and cold medications. However, therapeutic and toxicity data on serum and postmortem drug concentrations of these cough medications in children is limited and therefore difficult to interpret. Medication and/or dosing error could have played a role in some of the cases. In all cases, it is not clear how much of the active ingredients in the cough and cold medicines administered to the patient contributed to each of the patient's death.

- *2 cases had underlying bacterial infection, a confounding factor which could have partially or totally contributed to each of the patient's death.*
  - *case #1 had K. Pneumonia sepsis and elevated blood levels of pseudoephedrine, dextromethorphan and acetaminophen to at least 3x than expected.*
  - *case #4 had S. pneumonia meningitis and brompheniramine blood level of at least 2x than expected.*
- *3 cases had either compressional or positional asphyxia (of these, 1 was intentional)*
  - *case #2 had positional asphyxia. The mother was advised to give the infant Tylenol® for fever; investigation revealed Childrens Tylenol Plus-Cold and Cough cherry flavor on the kitchen counter. Therefore, it is clear that this infant was given the wrong preparation; a medication containing multiple active ingredients instead of a single-ingredient, and a children's syrup instead of an infant formulation. Pseudoephedrine blood level was higher (2x) than expected.*
  - *case #6 was a clear case intentional compressional asphyxia (Shaken Baby Syndrome). Although diphenhydramine was found in the blood, there was no history of cold symptoms or intake of cold medication. It is possible the child was given the medication to achieve sedation.*
  - *case #7 had compressional asphyxia due to overlay with pseudoephedrine and acetaminophen blood levels that are not elevated.*
- *2 cases had unknown cause of death*
  - *case #3 had ephedrine and pseudoephedrine (mildly elevated) in the blood.*
  - *case #9 had pseudoephedrine, dextromethorphan and acetaminophen in the blood which were not elevated.*
- *1 case (8) had SIDS, and had elevated pseudoephedrine level, 6x than expected.*
- *2 cases (5 & 10) had acute drug intoxication*
  - *case #5 had elevated pseudoephedrine level, 4x than expected.*
  - *case #10 had elevated pseudoephedrine level, 3x than expected. This was most likely intentional overdose to achieve sedation.*

[34] Ibid. p 521-2.
[35] Rumack 2004. Acetaminophen Misconceptions. Hepatology 2004;40: 10-15.

3) Boland DM, Rein J, Lew EO, and Lee Hearn W.
Fatal Cold Medication Intoxication in an Infant
Journal of Analytical Toxicology, Vol. 27, October 2003.

A two-month old black female who appeared to have a cold was crying until early morning, she was fed with a bottle containing water and a small amount of Tylenol®. She woke up 2½ hours later and was placed in a prone position with head to one side; 3 hours later, the child was unresponsive and was found dead. Items received by the Medical Examiner's Office included Infants' Pain Reliever Suspension Drops, Children's Pain Reliever, Q-Tussin Cough Formula, and two baby bottles: one with small amount of infant formula and one with pink-tinted liquid. An autopsy revealed pulmonary edema, no gross abnormalities of any organs and no evidence of traumatic injuries. Brompheniramine, dextromethorphan, and pseudoephedrine were qualitatively identified and quantitated in postmortem blood and liver specimens, as well as in the baby bottle containing the pink-tinted fluid. No drug was detected in the baby bottle containing the infant formula. The cause of death was listed as multiple drug intoxication (brompheniramine, dextromethorphan, and pseudoephedrine). The following is the toxicology result:

Table 13: Toxicology Results

Table I. Toxicology Results

Specimen	Brompheniramine	Dextromethorphan	Pseudoephedrine
Blood	0.40 mg/L	0.50 mg/L	14.4 mg/L
Liver	0.16 mg/kg	0.57 mg/kg	16 mg/kg
Bottle (white fluid)	ND*	ND	ND
Bottle (pink fluid)	1.4 mg total	9.4 mg total	40 mg total

* ND, not detected.

Comments: This patient's pseudoephedrine level was 14.4 mg/L (14,400 ng/mL), this level is at least 20x more than the reported therapeutic levels 0.18 to 0.50 mg/L (180 to 500 ng/mL)[36]. Therefore, this infant must have received a large amount of pseudoephedrine. The instructions on cough and cold products recommend asking a doctor for an infant this young. It is not specified if the mother asked for the doctor's advice before giving this medication; however, it appears from the report that the mother did not follow the instructions on the label and administered the medication through the baby bottle instead of using a dropper which would have delivered a much smaller amount. This is a clear case of drug overdose, probably unintentional.

[36] In pharmacokinetic studies of children aged 2 to 12 years (Simons FE, 1996), the Cmax of pseudoephedrine after therapeutic doses ranged from 180 ng/mL to 500 ng/mL, and were comparable to adults with the current dosing regimen (FDA, unpublished data)

4) **Joseph MM, King WD.**
Dystonic reaction following recommended use of a cold syrup.
Ann Emerg Med, Dec 1995; 26 (6): 749-51.

A 3-year old boy was brought to the ED due to abnormal movements. He had been previously healthy except for mild URI symptoms for which he received the appropriate dosages of cold syrup over 2 days. He was restless and exhibited arm flexion and leg extension and increased muscle tone. The patient was given charcoal 1 g/kg and 4 mL/kg of magnesium citrate. He did not respond to treatment with intravenous diphenhydramine. He was then given 0.02 mg/kg of IV benztropine[37], and the dystonic reaction resolved over a period of 5 minutes. Pretreatment drug screens of urine and gastric lavage aspirate were positive for diphenhydramine and phenylpropanolamine. The child was discharged home with no sequelae after 5 hours of observation.

Comments: *It is difficult to rule out the possibility that phenylpropanolamine was responsible for the patient's dystonic reaction. Although diphenhydramine has been used to treat this condition, it is probable that the antihistamine component of the cold syrup was responsible for the dystonic reaction.*

5) **Clark RF and Curry SC.**
Pseudoephedrine Dangers-Letters to the Editor
Pediatrics 1990; 85: 389-390.

A 19-month old previously healthy girl was brought to the ED 75 minutes after being found near an unlocked medicine cabinet with several 30-mg pseudoephedrine hydrochloride tablets in her mouth and several tablets spilled on the floor, at least 20 tablets were missing. The child vomited once before her arrival at the hospital, and her emesis contained several tablets. Upon arrival, she had widely dilated pupils, tremulous, agitated, and unable to be consoled by her parents. There was no evidence of respiratory distress. Her pulse was 200 bpm, systolic blood pressure was 75 mm Hg, respirations were 22, and rectal temperature was 37.9°C (100.2°F). The remainder of the examination was unremarkable. The child was given 12g of charcoal orally approximately 1 hour after arrival. Thereafter, she suffered a 60-second generalized tonic-clonic seizure which resolved spontaneously. She was loaded with antiseizure medications and suffered no further seizure activity. A urine drug screen was positive only for pseudoephedrine. Tachycardia resolved over 18 hours and was discharged in her normal state of health two days after admission.

Comments: *The authors stated that seizures have been reported in overdose situations of most sympathomimetics; however, the literature has not previously described convulsions with pseudoephedrine without mixed ingestions. This case was a clear unintentional overdose of pseudoephedrine.*

[37] Benztropine is a synthetic muscarinic-receptor antagonist that is structurally similar to atropine and diphenhydramine. It is used adjunctively with other antiparkinsonian agents to treat all types of parkinsonian syndromes including antipsychotic-induced extrapyramidal symptoms. (http://cpip.gsm.com/ accessed 7-16-07)

6) **Roberge RJ, Hirani KH, Rowland L, et.al.**
Dextromethorphan- and Pseudoephedrine-induced agitated Psychosis and Ataxia: Case Report
The Journal of Emergency Medicine 1999, Vol. 17 (2): 285–288.

A 2-year old male, 10.8 kg., with no significant prior medical history was brought to the ED with complaints that the child was acting bizarrely and "walking like he's drunk." The child had experienced upper respiratory symptoms two 2 days prior and received three doses of 1½ teaspoon Robitussin CF® cough preparation (pseudoephedrine 15 mg, with dextromethorphan, 7.5 mg/5 mL) every 6 hours on the day of admission only. He then developed hyperexcitability, irritability, incoherent babbling, and difficulty maintaining his balance. The physical examination was remarkable for hyperactivity, ataxia, dilated (4 mm) reactive pupils, and an initial tachycardia of 180 bpm. Toxicologic testing on blood drawn approximately 3.5 h after the last medication dose reported serum dextromethorphan (240 x 10^{-6} µg/mL) and pseudoephedrine levels (2.2 x 10^{-3} µg/mL). The child's status normalized over an observation period of 4 h in the ED, and he was discharged uneventfully.

Comments: The usual recommended dose listed in the monograph[38] for pseudoephedrine in adults is 60 mg every 4 to 6 hours (not to exceed 240 mg in 24 hours) and in children 2 to 6 years old, 15 mg every 4 to 6 hours (not to exceed 60 mg in 24 hours). For dextromethorphan, the recommended oral dose for in children 2 to 6 years old is 2.5 to 5 mg every 4 hours or 7.5 mg every 8 hours.[39] Some of the adverse events associated with the use of pseudoephedrine are: hallucinations, restlessness, psychosis, and seizures. For dextromethorphan, AEs associated with its use are: confusion, excitement, nervousness, restlessness, shaky movements, etc.[40] The patient was receiving 22.5 mg (instead of 15 mg) of pseudoephedrine every 6 hours, and 11.25 mg of dextromethorphan every 6 hours instead of 2.5 to 5 mg every 4 hours. This was a case of unintentional overdose of these medications and their known adverse effects.

7) **Wingert WE, Mundy LA, Collins GL, and Chmara ES.**
Possible Role of Pseudoephedrine and Other Over-the-Counter Cold Medications in the Deaths of Very Young Children
J Forensic Sci, March 2007 (52) No. 2: 487-90.

The Philadelphia Medical Examiners Office reported a series of 15 deaths between February 1999 and June 2005 of infants and toddlers 16 months and younger in which drugs commonly found in over-the-counter (OTC) cold medications were present. In each of the 15 cases presented, a young child was given OTC cold medication, presumably to treat or prevent symptoms from a cold or other respiratory condition. Table 8 summarizes the toxicology results according to age. The group was comprised of 12 males and 3 females (1 to 16 months old), 8 were born prematurely. The authors' discussion of the cases is as follows:

[38] 21 CFR 341.80
[39] 21 CFR 341.74
[40] Clinical Pharmacology Online (http://cpip.gsm.com/) accessed 8-8-07

- Pseudoephedrine was present in the blood or tissue of all of the cases and was the predominant drug detected. It was the only drug detected in 3 cases. The range of pseudoephedrine blood concentration (n=14) was 0.10–17 mg/L. (*The reported therapeutic levels for pseudoephedrine is 0.18 to 0.50 mg/L)*[41].
- Acetaminophen was present in the blood of each of the 5 cases: in 4 cases, blood concentrations were within the therapeutic range (<20 mg/L), and 1 case (#15) exceeded therapeutic levels.
- The following were also detected: dextromethorphan (5 cases), carbinoxamine (4 cases), chlorpheniramine (2 cases) and brompheniramine, doxylamine, and ethanol (one case each). In case #2, phenytoin was administered to control seizures and in case #14, phenobarbital has been previously prescribed.

In 8 of the 15 cases, (cases 3, 4, 9, 10, 11, 12, 14, and 15), the authors state that drug involvement was determined to be either the cause of death or a contributing factor, pseudoephedrine was the predominant drug. The cause of death for case #1 was listed as undetermined and case #2 as pneumonia, both cases had extremely high pseudoephedrine blood concentrations: 17 mg/L and 9.6 mg/L, respectively. It is probable that pseudoephedrine intoxication played a significant role in these infant deaths as well.

In cases 5, 6, and 7, the extent of drug involvement was unclear (pseudoephedrine levels was 0.22 to 0.36 mg/L). In case 8, co-sleeping with an adult was listed as a significant condition and in case 13 the cause of death was myocarditis; both had pseudoephedrine in the blood but not elevated.

[41] In pharmacokinetic studies of children aged 2 to 12 years (Simons FE, 1996), the Cmax of pseudoephedrine after therapeutic doses ranged from 180 ng/mL to 500 ng/mL, and were comparable to adults with the current dosing regimen (FDA, unpublished data)

Table 14: Case Histories

No.	Age/Gender	Drugs	Specimen*	Concentration†	Cause of Death/Manner of Death/Comments	History
1	2/M	Pseudoephedrine Pseudoephedrine Pseudoephedrine Dextromethorphan Dextromethorphan Dextromethorphan Carbinoxamine Carbinoxamine	Blood Liver Brain Blood Liver Brain Blood Liver	17.0 7.4 4.2 1.2 0.080 0.070 Present Present	Undetermined/ undetermined/very high pseudoephedrine levels detected	Full-term infant found unresponsive in baby seat by mother. One week history of cough, congestion, fever, diarrhea, and poor feeding. Evidence of past femur fracture. Infant previously in protective care and returned to mother 2 days before death. Autopsy finding significant for dehydration and microvescular hepatic steatosis
2	3/F	Pseudoephedrine Dextromethorphan Phenytoin	Blood Blood Blood	9.6 0.17 Present	Pneumonia/natural/very high pseudoephedrine concentration detected	Infant born 3 weeks premature. Brought to ER after a 3-day history of cough. Started on Viaxin previous day by pediatrician. At ER, child was found to be febrile with tachycardia and hypotension and phenytoin was given. Parents admitted to giving infant medication prescribed for older sibling. Autopsy significant for hepatic steatosis
3	3/M	Pseudoephedrine Pseudoephedrine Acetaminophen	Blood Liver Blood	1.6 1.1 <20.0	Sudden death associated with pseudoephedrine toxicity/undetermined	Infant born after 8-month gestation found dead in crib. Had cold-like symptoms. Reportedly given OTC Tylenol and Flu for the last 36 h. Autopsy unremarkable
4	5/F	Pseudoephedrine Brompheniramine	Cardiac blood Cardiac blood	6.4 0.34	Congenital heart disease/ undetermined/drug intoxication a contributing factor	Infant born after 32-week gestation found unresponsive at home with small amount of vomit in mouth. Caregivers gave no history of recent illness or medications. Autopsy significant for multiple heart defects: enlarged heart, double outlet left ventricle with subaortic ventricular septal defect and subpulmonic stenosis
5	4/M	Pseudoephedrine	Fluid off liver	0.36	SUID/natural	Full-term infant found unresponsive at home. Was in asystole and apenic upon arrival at hospital. Unable to resuscitate. Autopsy was unremarkable
6	2/M	Pseudoephedrine Dextromethorphan	Fluoridated blood Fluoridated blood	0.23 <0.05	Undetermined/ undetermined	Premature infant born after 27-week gestation found unresponsive in bed at home. Spent over 2 months in hospital after birth with a history of gastric reflux disease and breathing difficulties. Discharged 8 days before death. Current medications consisted of multivitamins and Metoclopramide. Autopsy significant for mild acute anoxic encephalopathy with no evidence of traumatic brain injury
7	4/M	Pseudoephedrine	Fluoridated blood	0.22	SUID/undetermined	Premature infant born after 34 weeks found unresponsive in crib at home. There was admission to giving medication but the symptoms prompting this were not specified. Autopsy was unremarkable
8	2/M	Pseudoephedrine Carbinoxamine	Fluoridated blood Fluoridated blood	0.30 <0.05	SUID/natural/overlie by cosleeping a contributing factor	Full-term infant found unresponsive in the same bed with parents. History of cough, cold, and wheezing 2 weeks before death and was prescribed antibiotics and Tylenol. Carbaxefed DM RF Oral Drops found at scene. Autopsy significant for acute anoxic encephalopathy
9	6/M	Pseudoephedrine Acetaminophen	Fluoridated blood Fluoridated blood	1.6 <10	Pseudoephedrine toxicity/ undetermined	Infant born after 34-week gestation. Spent 10 days in hospital after birth. Found face down with vomit on face. Mother reported infant having high fever in morning and admitted to administering antipyretics, fan therapy, and cool baths. Autopsy significant for adrenal hemorrhage and congenital asplenia
10	1/M	Pseudoephedrine Acetaminophen	Fluoridated blood Cardiac blood	0.34 <10	SUID/undetermined/ acute anoxic encephalomyopath and pseudoephedrine ingestion contributing factors	Full-term infant found unresponsive and face down in bassinet. Mother admitted to giving infant one-half dropper of Tylenol Plus to alleviate wheezing. OTC Concentrated Infant Drops Plus Cold retrieved at scene. Autopsy unremarkable except for anoxic encephalopathy
11	6/M	Pseudoephedrine	Fluoridated blood	0.44	Acute anoxic encephalopathy/ undetermined/ pseudoephederine in blood a contributing factor	Premature infant born after 27 weeks with heart defect that required surgical intervention. Found face down, rigid, apneic, and cold in bassinet by medics. Infant spent the first 3 months in hospital. Treated *c*. 1 month before death for esophageal reflux. Parents admitted to administering medication but symptoms that prompted treatment were not specified. Autopsy significant for acute anoxic encephalopathy
12	16/M	Pseudoephedrine Acetaminophen Chlorpheniramine Dextromethorphan Ethanol Ethanol Ethanol	Fluoridated blood Cardiac blood Fluoridated blood Fluoridated blood Fluoridated blood Fluid off liver Gastric contents	0.96 <10 0.069 0.050 0.034 0.023 1100	Anoxic encephalopathy/ undetermined/drug intoxication a contributing factor	Infant previously had been taken to emergency room with diarrhea, vomiting, and fever, where he was given Pedialyte and breathing treatment and discharged. Upon arrival at home, Medics found family member giving the infant CPR. Autopsy revealed anoxic encephalopathy
13	15/F	Pseudoephedrine	Blood	0.10	Myocarditis/natural	

Table 13 continued…

No.	Age/Gender	Drugs	Specimen*	Concentration†	Cause of Death/Manner of Death/Comments	History
						Infant had been vomiting at daycare center all day. Mother transported infant to hospital and baby treated for dehydration. Baby died at hospital short time later. Autopsy revealed myocarditis
14	4/M	Pseudoephedrine	Cardiac blood	1.0	Acute anoxic encephalopathy/ undetermined/drug poisoning a contributing factor	Full-term infant found unresponsive after afternoon nap. Previous hospital admission for pneumonia and brain bleed. Current medications included Phenobarbital. CarbaxefedDM RF Oral Drops and BromaxefedDM RF Syrup were found at scene. Autopsy revealed acute anoxic encephalopathy
		Chlorpheniramine	Cardiac blood	Trace		
		Carbinoxamine	Cardiac blood	Trace		
		Phenobarbital	Cardiac blood	<50		
15	3/M	Pseudoephedrine	Fluoridated blood	7.1	Drug poisoning/ undetermined	Premature infant born after 34 weeks found face down and lifeless when checked in the morning. No history of recent cough, cold, or fever. Parents denied administering any medication. History of Thrush and diaper rash, which was treated with oral and topical Nystatin. Autopsy revealed acute anoxic encephalopathy. Postmortem skeletal survey reveals a left tibial fracture
		Pseudoephedrine		120		
		Acetaminophen	Gastric contents	190		
		Dextromethorphan		0.39		
		Dextromethorphan	Fluoridated blood	40		
		Doxlyamine		1.0		
		Doxylamine	Cardiac blood	13		
			Gastric contents			
			Fluoridated blood			
			Gastric contents			

*Specimen information noted as documented during autopsy. Normal protocol was collection of blood from the cardiac area only.
†Blood concentrations=5 mg/L, liver and brain concentrations=mg/kg, ethanol blood concentrations=g%, gastric contents= mg/L.
SUID, sudden unexplained infant death.

Comments: A total of 13/15 of the deaths were patients ≤ 6 months who were found unresponsive by parents. Although parents did not report giving these medications in 9/15 cases, some medications were found in the bodies of all cases and pseudoephedrine was found in the body of all of the cases (0.10–17 mg/L). In 7/15 cases, pseudoephedrine levels were within the expected levels at therapeutic doses.

In 5 cases, the parents admitted that they had given the infant a cough/cold medication, a combination product was retrieved at the scene in these 5 cases. One case (#15) with a very high level of pseudoephedrine denied administering any medication. In some cases in which the levels of these medications are very high in the blood, it is clear that the child received excessive doses. The following cases had much higher blood levels of drugs than the reported levels at therapeutic doses in older children or adults:

- *Case #1: 2 months old, had 17 mg/L pseudoephedrine (34x higher than expected), dextromethorphan 1.2 mg/L (6x higher); 1 week history of cough, cold, congestion, fever, diarrhea, poor feeding, no mention of medications.*
- *Case #2: 3 months old, had 9.6 mg/L pseudoephedrine (19x higher than expected); cough for 3 days, parents admitted giving to infant medication (unspecified) prescribed to older sibling.*
- *Case #4: 5 months old, had 0.34 mg/L brompheniramine in cardiac blood (15x higher than expected); no history of illness or medication.*
- *Case #15: 3 months old, had 7.1 mg/L pseudoephedrine (14x higher than expected); no history of cough, on Nystatin for oral thrush, denies other medications.*

Although cough/cold medications were present in the bodies of these patients, it cannot be determined how much the active ingredient in these medications contributed to each of the patient's death. Deaths were mostly confounded either with an underlying medical illness (such as cardiac), or respiratory infection at the time of death. Deaths could also have been due to other conditions such as sudden infant death syndrome (SIDS) which is most common in infants, child abuse, compressional asphyxia, sepsis, etc. and that administration of cough/cold medication was coincidental. Toxic and therapeutic levels for most of these drugs are unknown in children and postmortem results are therefore difficult to interpret.

IV. Statements from Different Organizations

A. The American Academy of Pediatrics (AAP)

In 1997, the AAP Committee on Drugs published an article on the use of codeine and dextromethorphan-containing cough remedies in children and has the following conclusions and recommendations:[42]

1) No well-controlled scientific studies were found that support the efficacy and safety of narcotics (including codeine) or dextromethorphan as antitussives in children. Indications for their use in children have not been established.
2) Suppression of cough in many pulmonary airway diseases may be hazardous and contraindicated. Cough due to acute viral airway infections is short-lived and may be treated with fluids and humidity.
3) Dosage guidelines for cough and cold mixtures are extrapolated from adult data and clinical experience, and thus are imprecise for children. Adverse effects and overdosage associated with administration of cough and cold preparations in children are reported. Further research on dosage, safety, and efficacy of these preparations needs to be done in children.
4) Education of patients and parents about the lack of proven antitussive effects and the potential risks of these products is needed.

On the AAP website, under parenting corner, parents are instructed to never use cough/cold preparations in a child under 3 years of age unless prescribed by their pediatrician.

B. American College of Chest Physicians (ACCP)

In 2006, ACCP published guidelines for evaluating chronic cough in pediatrics in the Cardiopulmonary and Critical Care Journal (CHEST) and listed a summary of recommendations. It is to be noted that this publication specifically addresses chronic cough and not acute cough due to the common cold. There is one out of the 13 recommendations that pertains to acute cough and it recommends: "In children with cough, cough suppressants

[42] Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children. Committee on Drugs. Pediatrics 1997; 99; 918-920.

and other OTC cough medicines should not be used, as patients especially young children, may experience significant morbidity and mortality".

C. World Health Organization

In 2001, the World Health Organization published an article entitled "Cough and Cold Remedies for the Treatment of Acute Respiratory Infections in Young Children"[43] and have the following recommendations for management of a simple cough or cold or sore throat: Health workers can safely recommend:

- Oral hydration.
- Relief of nasal congestion when it interferes with feeding; saline nose drops can be tried.
- Use of paracetamol for reduction of high fever when this distresses the child and for relief of pain.
- Safe, soothing remedies (e.g. simple linctus[44]) are useful for both a cough and sore throat.
- Children with signs suggesting pneumonia should immediately be taken to a health worker for assessment.
- Although they have a role in symptomatic relief of recurrent allergic rhinitis, antihistamines are not indicated for relief of nasal congestion due to the common cold.
- Cough and cold remedies other than saline nose drops should not be given to young infants (less than 2 months old), or to exclusively breastfed infants (aged up to 4–6 months).
- There is no evidence that antibiotic or other medical therapy prevents pneumonia; Antihistamines and sympathomimetics do not reduce the incidence of otitis media or prevent of eustachian tube dysfunction following a cold.

V. SUMMARY AND COMMENTS

The commonly used active ingredients in cough and cold preparations in children were classified as "generally recognized as safe and effective" for human use through the OTC monograph process. This classification was based on review by an expert external advisory review panel of the safety and efficacy data. Pediatric dosing was based on extrapolation from adult doses and was calculated as a fraction of the usual adult dose based on the child's age (see table A-1): under 2 years of age - ask a doctor; 2 to 6 y/o - ¼ of the adult dose; 6 to 12 y/o - ½ of the adult dose. This extrapolation is based on the assumption that the pathophysiology of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients. There are no dosing recommendations listed for children < 2y/o in the monograph. The labels for OTC cough and cold medicines direct consumers to ask a doctor for dosing directions in children <2 years old; hence, the dosing and use of these drugs is left to the discretion of the physician. Physicians extrapolate dosing in this population from adult doses and older children based on the weight or age of the child, or refer to the manufacturer's dosing recommendations, textbooks, pediatric handbooks (e.g. The Harriet Lane Handbook) or

[43] Department of Child and Adolescent Heath and Development, World Health Organization (WHO), 2001
[44] Linctus-defined as a syrupy liquid medicine, taken by mouth to relieve coughs and sore throats (http://www.allwords.com/word-linctus.html).

drug information handbooks. It is not clear how dosing for children <2 y/o was determined by these references.

The literature search resulted in 11 clinical trials involving children using cough and cold medications published in the last 50 years (1951 to 2004). See Table A-3 in the Appendix section for a summary of the characteristics of these clinical studies.

- With regard to drug class used:
  - 3 studies involved the use of antitussives (dextromethorphan used alone or in combination with other active ingredients)
  - 3 studies involved the use of antihistamines
  - 5 studies used combination products (including 2 studies involving the use of pseudoephedrine alone or in combination with other drug).

- With regard to the indication studied, cough was the most frequently studied symptom. Four studies specifically evaluated cough (2 studies on night cough); 2 studies evaluated symptoms related to allergies; 1 study evaluated rhinorrhea; and 4 studies evaluated URI/cough and cold symptoms.

- There were conflicting results from the studies conducted using cough and cold medications in children. Of the 11 clinical studies in children, the following 4 studies claimed efficacy: Weipple (1984), McGovern (1959), Lipschutz (1960), and Reece (1966). The other studies did not claim efficacy: Fisher (1951), Sakchainanont (1990), Korppi (1991), Hutton (1991), Taylor (1993) Clemens (1997) and Paul (2004).

- The studies in children have one or more of the following areas of concern:
  - Some studies lacked a placebo arm; others did not mention randomization or blinding.
  - It is not clear if the studies were adequately powered to show a difference between the drug and placebo.
  - The number of participants in each study was small, the age ranges of participants in each study were too wide and varied among studies, and the number of participants in each age range is not known.
  - Some of the studies were conducted in exclusively white or black population only.
  - The inclusion and exclusion criteria varied among the studies for the same drug class. The eligibility criteria may allow inclusion of subjects with symptoms that are not severe or frequent enough to detect a treatment effect.
  - The active ingredients from each class of drugs were administered in different doses and dosing frequencies.
  - In some studies, the dose and/or dosing frequency may not be adequate to elicit the effect of the drug.
  - The duration of treatment varied from a single dose to a multiple-dose treatment for 2 or 3 days, or up to 18 months.
  - In some studies, symptom(s) evaluated were not related to the expected therapeutic effect of the drug and therefore may not have benefited from the treatment.

- Outcome measurement and assessment varied; most studies used subjective reporting of symptoms (e.g., rhinorrhea, nasal congestion, or cough) by using symptom severity scores, answering questionnaires, recording with a use of a diary, use of a tape recorder or assessment by a physician/investigator. None of the studies specified if the outcome measures used were validated.
- The severity of each symptom at baseline were not provided in some studies and symptom improvement was not clearly defined.
- The full categories in the symptom rating scale were not provided in some studies. A detailed description of the symptom rating scale and definitions of the different categories in the scale were not provided in most studies.
- The timing of measurement of symptoms is an issue in some of the studies; this may have affected efficacy assessment. The timing of evaluation of the effect of the test drug did not occur when the efficacy of the drug was expected to occur.
- Compliance was not guaranteed nor mentioned in some of the studies.
- Some of the active ingredients tested are no longer marketed in the U.S.
- Some of the studies were conducted at least 40 years ago and therefore were done under a different standard.
- Symptoms of cough and cold generally improve with time, therefore it may be difficult to show a treatment effect for some of the endpoints measured.

- The study by Reece (1966) was used to evaluate the effectiveness of dextromethorphan and the Lipschutz (1960) study was used to support the effectiveness of pseudoephedrine in children in the monograph. The study by McGovern (1959) was referenced in evaluating the effectiveness of brompheniramine in the monograph in children.[45]

- There were no reported deaths or serious adverse effects from the published clinical studies despite higher than monograph recommended doses in certain age groups in some studies. The adverse events reported were mostly mild; drowsiness was the most common reported adverse event. However, some studies did not report adverse effects adequately.

There were 7 articles on case reports or case series associated with the use of OTC cough and cold medications.

- The case series/reports have the following in common:
  - Serious adverse events and/or deaths associated with the use of cough/cold medication are reported in children, mostly in infants. These occurred mostly due to medication error leading to overdose.
  - Most patients who died had a detectable or increased blood levels of cough and cold medications, mostly pseudoephedrine. It is not clear in some cases how much of these medicines were administered to the child. In some cases, parents denied or were not aware of the active ingredients contained in the product given to the child.
  - The reported deaths and serious adverse events are mostly confounded with either an underlying medical illness or interaction with other drugs.

[45] Advance Notice of Proposed Rule (ANPR) 41FR p.38312, 9-9-76.

- Deaths could have been due to other conditions such as sudden infant death syndrome (SIDS), child abuse, and the administration of cough/cold medication could have been coincidental.
- For most drugs, therapeutic and toxic levels are unknown in children, and postmortem levels may be difficult to interpret.
- The contribution made by the active ingredients in these cough and medications to the adverse event or death of a patient is difficult to assess.

- Elevated levels of cough and cold medications in the blood/body could have been due to one of the following:
  - Parents misunderstanding or misinterpreting the recommended dose, dosing frequency or length of therapy.
  - Parents being unaware that they are giving a medication that contains more than one active ingredient.
  - Parents unintentionally administering combination products with duplicate active ingredients.
  - Using an incorrect measuring device [e.g., giving 1 teaspoon (5 mL) instead of 1 dropper (1 mL) for concentrated formulations].
  - Parents administering a preparation intended for adults or older sibling to an infant.
  - Parents increasing the dose, or giving adult preparations that may be perceived as a stronger preparation.

The literature search also resulted in two articles that reviewed clinical trials in children on cough and cold medications. The article by Schroeder and Fahey, 2004 (Cochrane Review) on randomized controlled trials comparing oral OTC cough preparations to placebo in children and adults suffering from acute cough. The authors concluded that there is no good evidence for or against the effectiveness of OTC medicines in acute cough. Another article (Smith 1993) that evaluated OTC cold medications concluded that there is no good evidence demonstrating the effectiveness of OTC cold medications in preschool children. Most of the studies reviewed in these review articles were similar those included in this review. Both of these review articles concluded that further studies are needed to evaluate the efficacy of these medications in children.

Guidelines by the American Academy of Pediatrics (AAP) instruct parents not to use cough and cold preparations in children under three years of age unless prescribed by their pediatrician; the age cut-off of three years is not clear. The AAP and American College of Chest Physicians (ACCP) do not recommend the use of cough suppressants in children and emphasize educating parents on the effect of these drugs. The World Health Organization (WHO) recommends non-pharmacological therapy for the simple cough or cold.

VI. CONCLUSION

- Based on the review of published clinical trials in children (1½ months to 18 years old), there is no convincing evidence of efficacy of cough and cold medications when used to treat symptoms of the common cold in this population. However, it is important to note

that there were issues with the design of the studies such as: definition and timing of treatment outcomes, adequacy of dose, dosing frequency, and duration of therapy. It is also possible that the studies were not adequately powered to show a difference between the drug and placebo.

- The overall incidence of reported serious adverse events from these drugs is low despite their widespread use. These medications are generally safe when used appropriately and at the recommended dose and dosing frequency as evidenced by the absence of serious adverse events or deaths in all published clinical studies involving children 6 months to 18 years old.

- Excessive levels of these medications in the blood from patients (from case reports) who died or had serious adverse events were mostly due to dosing and/or administration errors by caregivers.

- Cough is a symptom that could be measured objectively; studies using a cough-counting technique would be very useful.

- Other cold symptoms such as nasal congestion and rhinorrhea are difficult to assess especially in children because these are subjective outcome measures. Although possible, pediatric clinical studies are more difficult to conduct because children are less verbal or are unable to express their symptoms well; therefore, one has to rely on the caregiver for assessment of symptoms.

- In conducting clinical studies evaluating symptoms of cold in children, the following are important to consider:
  - precise and well-defined outcome measures
  - frequently measured symptoms
  - measurement of treatment outcomes at the time of the expected efficacy of the drug
  - a time interval from initiation of therapy to the follow-up interview that is not too long or that occurs within a reasonable time
  - symptoms from the common cold are believed to be generally self-limiting, may peak within 2 to 3 days after infection, and may have profound response to placebo.

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APPENDIX

Table A-1: Current Monograph Pediatric Dosing
Antihistamine/Antitussive/Nasal Decongestant (21 CFR 341)
Commonly Used Active Ingredients in Cough and cold Medications

Category/ Ingredients	Age-Based Dosing			
	Adults and Children ≥ 12 y/o	**Children 6 to 12 y/o**	**Children 2 to 6 y/o**	**Children < 2 y/o**
Antihistamine				
Brompheniramine Maleate	4 mg q 4-6 hours, not to exceed 24 mg/24 hrs or as directed by a doctor	2 mg q 4-6 hrs, not to exceed 12 mg/24 hrs or as directed by a doctor	Consult a doctor ***1 mg q 4-6 hrs, not to exceed 6 mg/24 hrs***	
Chlorpheniramine Maleate	4 mg q 4-6 hrs, not to exceed 24 mg/24 hrs or as directed by a doctor	2 mg q 4-6 hrs, not to exceed 12mg/24 hrs or as directed by a doctor	Consult a doctor ***1 mg q 4-6 hrs, not to exceed 6 mg/24 hrs***	
Diphenhydramine Hydrochloride	25 to 50 mg q 4-6 hrs, not to exceed 300 mg/24 hrs or as directed by a doctor	12.5 to 25 mg q 4-6 hrs, not to exceed 150 mg/24 hrs or as directed by a doctor	Consult a doctor ***6.25 mg q 4-6 hrs, not to exceed 37.5 mg/24 hrs***	
Triprolidine HCl	2.5 mg q 4-6 hrs, not to exceed 10 mg/24 hrs or as directed by a doctor	1.25 mg q 4-6 hrs, not to exceed 5mg/24 hrs or as directed by a doctor	**4 to 6 y/o:** ***0.938 mg q 4-6 hrs, not to exceed 3.744 mg/24 hrs*** **2 to 4 y/o:** ***0.625 mg q 4-6 hrs not to exceed 2.5 mg/24 hrs***	**4 mos to 2y/o**: ***0.313 mg q 4 to 6 hrs not to exceed 1.252 mg/24 hrs***
Antitussive				
Dextromethorphan	10 to 20 mg q 4 hrs or 30 mg q 6-8 hrs, not to exceed 120 mg/24 hrs or as directed by a doctor	5 to 10 mg q4 hrs or 15 mg q 6-8 hrs, not to exceed 60 mg/24 hrs or as directed by a doctor	2.5 to 5 mg q 4 hrs or 7.5 mg q 6-8 hrs, not to exceed 30 mg/24 hrs or as directed by a doctor	Consult a doctor
Diphenhydramine Hydrochloride	25 to 50 mg q 4-6 hrs, not to exceed 300 mg/24 hrs or as directed by a doctor	25 mg q 4 hrs, not to exceed 150 mg/24 hrs or as directed by a doctor	Consult a doctor ***6.25mg q 4 hrs, not to exceed 37.5 mg/24 hrs***	
Nasal Decongestant				
Pseudoephedrine	60 mg q 4-6 hrs, not to exceed 240 mg/24 hrs	30 mg q 4-6 hrs, not to exceed 120 mg/24 hrs	15 mg q 4-6 hrs, not to exceed 60 mg/24 hrs	Consult a doctor
Phenylephrine Hydrochloride	10 mg q 4 hrs, not to exceed 60 mg/24 hrs	5 mg q 4 hrs, not to exceed 30mg/24 hrs	2.5 mg q 4 hrs, not to exceed 15 mg/24 hrs	Consult a doctor
Expectorant				
Guaifenesin	200 to 400 mg q 4 hrs, not to exceed 2400 mg/24 hrs	100 to 200 mg q 4 hrs, not to exceed 1200 mg/24 hrs	50 to 100 mg q 4 hrs, not to exceed 600 mg/24 hrs.	Consult a doctor

*Professional labeling 21 CFR 341.90

Table A-2: Cold, Cough, Allergy Drug Products for OTC Use
(21 CFR 341)

Antihistamines (21 CFR 341.12)	**Antitussives** (21 CFR 341.14)	**Expectorant** (21 CFR 341.18)	**Nasal decongestants** (21 CFR 341.20)
Brompheniramine maleate. Chlorcyclizine HCl Chlorpheniramine maleate Dexbrompheniramine maleate Dexchlorpheniramine maleate Diphenhydramine citrate Diphenhydramine HCl Doxylamine succinate Phenindamine tartrate. Pheniramine maleate Pyrilamine maleate Thonzylamine HCl Triprolidine HCl	Oral Chlophedianol HCl Codeine ingredients Dextromethorphan Dextromethorphan HBr Diphenhydramine citrate Diphenhydramine HCl Topical Camphor Menthol	Guaifenesin	Oral Phenylephrine HCl Pseudoephedrine HCl Pseudoephedrine sulfate Topical Levmetamfetamine Ephedrine Ephedrine HCl Ephedrine sulfate Naphazoline HCl Oxymetazoline HCl Phenylephrine HCl Propylhexedrine. Xylometazoline HCl

Table A-3: Characteristics of Clinical Studies on Cough and Cold Preparations

Study	Population	Indication	Treatment	Frequency and Duration	Measure of Outcome	Efficacy (Author's Findings)	Adverse Effects
Antitussives							
Paul et al. 2004 (U.S.A.)	2 y/o -18 y/o (N=100)	Night cough due to URI	-**Dextromethorphan:** (**DM**, n=33) 2-5 y/o = 7.5 mg/dose 6 -11 y/o = 15 mg/dose 12-18 y/o = 30 mg/dose. -**Diphenhydramine:** (**DPH**, n=33) 1.25 mg/kg/dose -**Placebo** (n=34)	Single dose for 1 night	Parent Questionnaire 7-point Likert scale (6=constant, 0=not at all)	Active treatments no different than placebo	-Hyperactivity in all treatment arms -Insomnia in DM arm -Drowsiness in DPH arm
Taylor et al. 1993 (U.S.A.)	18 mo-12 y/o (N=49)	Night cough due to URI	- **Guaifenesin** 100mg **+ Dextromethorphan** 15mg, per 5 ml (**DM**, n=19) - **Guaifenesin** 100mg **+ Codeine** 10mg, per 5ml (**Cod**, n=17) - **Placebo** (**PL**, n=13) Dose:18 mo - 5 y/o: 2.5 ml 6 -11 y/o: 5 ml	Single dose at bedtime for 3 nights	Parent questionnaire, cough score (0-4) 0=none, 4=very often	-Active treatments no different than PL on any day -Reduction in cough score was pos. correlated with severity at start of treatment. -Cough score decreased on day 3 regardless of treatment	Drowsiness -3 Placebo -3 DM Diarrhea -3 PL -1 Cod -1 DM Hyperactivity -2 DM -3 Cod
Korrpi et al. 1991 (Finland)	1 y/o -10 y/o (N=75)	Respiratory infection w/ cough	-**Dextromethorphan** 1.5 mg/ml (**D**) (n=24) -**Dextromethorphan** 1.5 mg/ml **+ Salbutamol** 0.2 mg/ml (**DS**) (n=25) -**Placebo** (n=26) Dosage: <7 y/o = 5 ml t.i.d. >7 y/o = 10 ml t.i.d.	3x/day for 3 days	Parent Questionnaire cough symptom score (0-3) 0=no, 1=mild, 2=moderate, 3=severe	No difference in cough symptom scores between the 3 groups on any 3 days.	Low side effects, no detailed info.

Study	Population	Indication	Treatment	Frequency and Duration	Measure of Outcome	Efficacy (Author's Findings)	Adverse Effects
Antihistamines							
Sakchainanont et al. 1990 (Thailand)	1.5 mo - 5 y/o (N=143)	Rhinorrhea of 3 days	-**Clemastine fumarate** 0.05 mg/kg/day, 2x/day (am, evening) (n=48) -**Chlorpheniramine maleate** syrup 0.35 mg/kg/day, 3x/day (n=48) -**Placebo** (n=47)	2-3x/day for 3 days	Parent & investigator symptom score (0-3) (3=severe sx, 2=moderate, 1=mild, 0=no sx) Evaluated: cough, nasal discharge, nasal turbinates	-Improvement of symptoms in all groups. -No significant difference between groups. -Clemastine significantly improved character of nasal discharge.	Sedation: antihistamines no different than placebo.
McGovern et al. 1959 (U.S.A.)	2mo -14 y/o (N=200)	Allergic symptoms	**- Parabromdylamine maleate (Brompheniramine)** 2m-2y: 0.2 mg/lb/24 hr ÷ 3 doses, (n=73) 2y-6y: 0.2 mg/lb/24 hr (n=70)* 6y-14y: 0.15 mg/lb/24 hr (n=57)* * frequency not specified ***(No placebo arm)***	3x/day for 18 mos.	Nasal symptom improvement (good, fair, or poor)	Effective antihistaminic agent. Effective dose: 0.2 to 0.5 mg/lb/24 hrs.	Very low incidence of undesirable side effects (no details) Drowsiness reported.
Fisher 1951 (U.S.A.)	9 y/o -16 y/o (N=74)	Common cold	-**Tripelennamine HCl**: (n=37) ≥12 y/o: 50 mg 4x/day <12 y/o: 25 mg 4x/day -**Placebo** (n=37)	4x/day for 48 hours	Symptom improvement, standardized form used	Tripelennamine proved no more effective than a placebo in the treatment and prevention of the common cold in its early stages.	Drowsiness for both groups (no details)
Combination							
Clemens 1997 (U.S.A.)	6 mo to 5 y/o (N=59)	URI symptoms	-**Brompheniramine** 2 mg **+ PPA** 12.5 mg, per 5ml (n=28) 6 m -2y: ½ tsp q 4 hrs. 2 y/o - 5 y/o: 1 tsp q 4 hrs. -**Placebo** (n=31)	q 4 hrs as needed for 48 hrs (max of 4 doses)	Parent Questionnaire 7-point Likert scale (much worse to much better)	-No difference between the ADC and placebo group in symptom improvement. -ADC group slept better after 2 hrs.	Not reported

Study	Population	Indication	Treatment	Frequency and Duration	Measure of Outcome	Efficacy (Author's Findings)	Adverse Effects
Weipple, 1984 (Austria)	≥ 4 y/o (N=56)	Cough & cold symptoms	-**SCH 399 syrup**: (n=29) azatadine maleate 1 mg + pseudoephedrine SO_4 60 mg + dextromethorphan HBr 20 mg -**Expectorant syrup**: (n=27) Diphenhydramine HCl 0.205 g + NH4Cl 2 g + sodium citrate1g + menthol 0.017 g. Dosage: 4 - 6 y/o = 1/2 tsp 3x/day 6 -12 y/o = 1/2 tsp 4x/day ***(No placebo arm)***	3 to 4x/day for 5 days	-Symptom score (0-3) for parents, & -Symptom improvement grading by physician (≥75% improv't to poor (<30%)	Patients treated with SCH 399 experienced a significantly greater degree of relief compared to the Expectorant syrup.	No clinically important changes in vital signs were observed in either group throughout the study.
Reece et al. 1966 (U.S.A.)	Inpatient: (N=22) 2 m- 9 y/o A: n=7 B: n=8 C: n=7	Acute respiratory infection w/ cough	- **A: Triaminicol** syrup, each 5 ml: PPA 12.5 mg + Pheniramine maleate 6.25 mg + Pyrilamine maleate 6.25 mg + Dextromethorphan HBr 15 mg + Ammonium chloride 90 mg **-B: Dorcol** Cough syrup, each 5 ml Dextromethorphan HBr 7.5 mg + PPA HCl 8.75 mg + Glyceryl guiacolate 37.5 mg + Alcohol 5% -**C: Placebo** syrup Dose: <2 y/o: 1.25 ml (A), 2.5 ml (B,C) 2 to 6 y/o: 2.5 ml (a), 5 ml (B,C) 7 to 12 y/o: 5 ml (A), 10 ml (B,C)	Inpatient: every 8 hrs x 5 doses	Inpatient: recorded cough at night using a tape-recoder	Inpatient: Both antitussive syrups containing dextromethorphan, provided an antitussive effect for up to 8 hrs better than placebo	Not reported
	Outpatient: (N=43) 2m to 12 y/o A: n=16 B: n=13 C: n=14	Cough		Outpatient: dosing not specified Tx duration & dosing frequency unclear.	Outpatient: Mother reported symptoms using a standard form	Outpatient: Antitussive response to all 3 products was satisfactory.	
Lipschutz 1960 (U.S.A.)	4 m-17 y/o (N=200)	Respiratory allergic & non-allergic diseases	-**Triprolidine + pseudoephedrine** Allergic (n=25), Non-allergic (n=49) -**Pseudoephedrine** Allergic (n=17), Non-allergic (n=65) -**Placebo** Allergic (n=10), Non-allergic (n=34) Dose not specified.	4x/day for 3 days	Patients drug response (excellent, good or poor). Responder was not specified.	Pseudoephedrine, with or without triprolidine, gives satisfactory results, in 90% of the non-allergic conditions and in 70% of non-allergic conditions.	No adverse effects.

Study	Population	Indication	Treatment	Frequency and Duration	Measure of Outcome	Efficacy (Author's Findings)	Adverse Effects
Hutton et al. 1991 (U.S.A.)	6 m-5 y/o (N=84)	Common cold	-**Dimetapp**® antihistamine-decongestant, each 5 ml contains: Brompheniramine maleate 4 mg Phenylephrine hcl 5 mg Phenylpropanolamine hcl 5 mg Dosage: calculated by wt to achieve a Brompheniramine dosage of 0.5 to 0.75 mg/kg/day, divided 3x/day. (n=30) -**Placebo** (n=24) -**No treatment** (n=30)	3x/day for 2 days	Parental report of symptoms (0 to 3) 0=not at all, 1=occasionally, 2=frequently, 3=all the time	-No difference in symptom improv't regardless of treatment. -Parents who believed their children needed medicine reported greater improv't at 48 hrs regardless of treatment.	Loose stools -1 placebo Hyperactivity -1 drug Sleepier than usual -1 drug

DM-dextromethorphan
PL-placebo
Sx-symptoms
Tx-treatment

Cold/Cough Advisory Committee meeting, Oct. 18-19, 2007

CLINICAL PHARMACOLOGY REVIEW

Executive Summary

FDA received a Citizen Petition questioning the safety and efficacy of over-the-counter cough and cold drug products in children less than 6 years of age. There are reports of deaths of infants and toddlers in the medical literature in which drugs commonly found in OTC cough and cold preparations were detected at very high concentrations. The petition specifically pointed out the absence of any dosing recommendation on the label for children under the age of 2, raising safety concerns for children in an age range highly vulnerable to overdose.

Cold and cough products under discussion are regulated under both the over-the-counter (OTC) monograph and new drug applications. The monograph supports safety and efficacy of these products while providing dosing guidance and directions for use. For decongestants, antihistamines, expectorants and antitussive ingredients, the children's doses were determined by taking ½ the adult dose for children 6 to 12 years of age and ¼ the adult dose for children 2 to 5 years of age except for antihistamines, in which the dosing in children only goes down to 6 years of age. Incidentally, the monograph approximately follows dosing based on adjustments for average bodyweight for age intervals of 2-5 years and 6-11 years.

From the clinical pharmacology perspective, this review attempts to address the following broad topics: 1) scientific rationale for the current practice of monograph recommended pediatric dosing of a fraction of adult dose, 2) current standard for pediatric dosing recommendation based on PK/PD, 3) impact of developmental physiology on drug disposition in children, 4) inadequacy of PK data for cough and cold drugs in young children.

The effectiveness in children (age 2 – 12) of OTC cough and cold drugs was mainly based on an extrapolation of adult efficacy data and recommendation by external experts. For many prescription products, FDA has often extrapolated efficacy data from adults to children using PK/PD bridging approach where the clinical response and pharmacologic intervention are expected to be similar to the adult population, based on a good understanding of the pathophysiology of the disease. From the limited pharmacokinetic data available to the FDA, it appears that pseudoephedrine (decongestant) and chlorpheniramine (anti-histamine) exhibit lower systemic exposure in children compared to adults following monograph dosing. Therefore, it is apparent that dosing adjustment by body weight may not be able to entirely predict the extent of PK differences between adults and children for these drugs.

During child development particularly in the first two years of life, physiological and biochemical processes governing drug absorption, distribution, metabolism and excretion

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undergo significant maturation and growth. Clearance has been identified as one of the key pharmacokinetic parameters that determine drug exposure and pharmacological response. The ontogeny of systemic clearance mechanisms (renal and hepatic) is believed to be the most critical determinant of a pharmacological response in the developing infant. Renal clearance processes are believed to be immature at birth and this immaturity is thought to persist for several months to several years before they approach adult values. Cytochrome P450s (CYPs) 3A4/5 and 2D6 appear to be the two principal enzymes responsible for the metabolism of commonly used cough and cold medications. A recent publication by Blake et al. 2006 illustrated the developmental changes in CYP2D6 and CYP3A4 *in vivo* expression and activity over the first year of life by examining the ontogeny of dextromethorphan biotransformation, a widely used cough suppressant in the OTC monograph.

Excessive post-mortem levels of cough and cold medications in recent reports of deaths in young children could not be easily explained by common causes of drug overdose and drug interaction. The phenomenon of drug redistribution following death has been considered as a contributing factor for such high post-mortem levels. Various factors such as the site of postmortem blood collection, timing of collection after death, type of biological matrix, sample processing have been known to influence the measurement of post-mortem drug concentration. Several common OTC cold and cough drugs have been found to undergo postmortem redistribution, therefore, likely to have some contribution towards such high levels of these drugs in post-mortem blood samples in children.

Based on the available PK data on pseudoephedrine and chlorpheniramine in children, extrapolation of pediatric dosing of a fraction of adult dose roughly adjusted for bodyweight appears to be insufficient. Following FDA's decade long pediatric initiatives, relevant clinical studies specifically gathering pharmacokinetic and safety information in children had been conducted as a result of which improvements in pediatric information in the drug labeling including age-appropriate dosing, were achieved for a number of drugs across several therapeutic areas. Robust and well-designed pharmacokinetic studies that are needed for pediatric dose optimization are currently lacking for cough and cold medications. These studies should, at a minimum, attempt to obtain pharmacokinetic data at different age groups, especially in children 2 years and younger with the application of limited PK blood sampling strategy. Provided disease progression and clinical response between pediatric and adult population are similar, these PK studies coupled with safety may be sufficient to propose dosing recommendations in children based on modeling and simulation techniques.

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Introduction

FDA received a Citizen Petition requesting that the Agency take action re-labeling cough and cold products under the OTC monograph to say that they have not been found to be safe or effective in children under the age of 6 for the treatment of cough and cold and recommending that these products should not be used in this age group. There are reports of deaths of infants and toddlers in the recent past (Gunn VL et al. 2001, Marinetti L et al. 2005, Wingert WE et al. 2007, Sharfstein JM) in which drugs commonly found in OTC cough and cold preparations were detected at very high concentrations. The petition also pointed out the absence of any dosing recommendation on the label for children under the age of 2. The label recommends parents to consult the doctor for dosing information as a result of which physicians prescribe doses without any demonstrated evidence of efficacy and/or safety in this age group. This empirical dosing approach raises safety concerns for children in an age range highly vulnerable to overdose.

Cold/cough medications are primarily regulated under the over-the-counter (OTC) monograph process, which provides for permissible active ingredients that are found to be generally safe and effective (GRASE) and can be combined with acceptable labeling, including directions for use. For decongestants, expectorants and antitussive ingredients, the children's dose was determined by taking ½ the adult dose for children 6 to 12 years of age and ¼ the adult dose for children 2 to 5 years of age except for antihistamines in which the dosing in children only goes down to 6 years of age. The average body weights for children 6 to 11 years of age and 2 to 5 years of age are about 30 kg (range: 21-41 kg) and 17 kg (range: 13-21 kg), respectively. Assuming an average adult body weight of 60 kg, these weights for children were approximately ½ and ¼ of the average adult weight although as in adults, wide variation in individual bodyweights was noted in children within these age intervals. Therefore the OTC monograph for these drug products roughly follows dosing based on adjustments for average bodyweight for these age groups. This method of extrapolation was recommended by external expert panels convened to review the safety and efficacy data for the ingredients included in the OTC monograph review.

In the absence of efficacy studies in pediatric populations that are inherently difficult to conduct in children, FDA's current standard for dosing recommendation in pediatrics is based on achieving systemic exposure in pediatrics comparable to adults with the demonstration of adequate safety in children [refer to FDA Guidance for Industry (2003) Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications]. This paradigm is only possible if the disease progression and clinical response in pediatric and adult population are generally believed to be similar, based on a good understanding of the pathophysiology of the disease and drug dose and/or concentration response relationship for efficacy (Figure 1). For example, the dosing recommendation for second generation antihistamines in children for the treatment of allergic rhinitis was obtained by way of extrapolating from adult doses using PK data.

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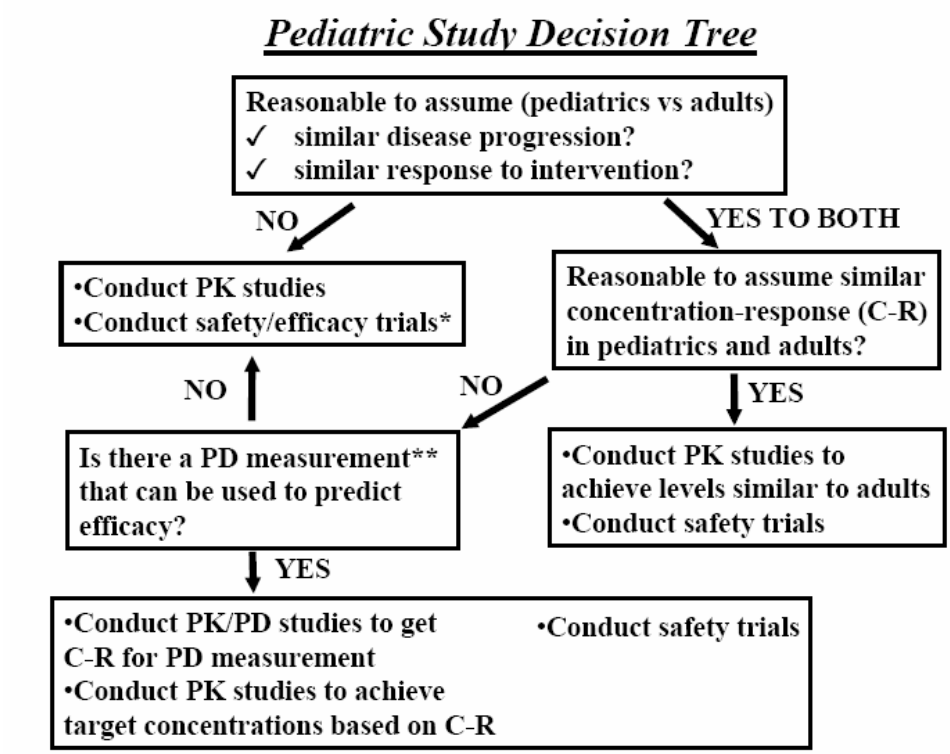

Figure 1. FDA proposed decision tree for conducting clinical studies in children *(reference: FDA Guidance for Industry (2003) Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications)*

With the recent Citizen Petition questioning the safety and efficacy of these products in children under the age of 6 for the treatment of cough and cold, it is worthwhile to review the pharmacokinetics of some of these compounds in children of different ages in comparison to adults. This allows one to evaluate the appropriateness of monograph dosing of these drugs in children on the basis of equivalent systemic exposure between adults and children. Two common cold/cough medications, namely pseudoephedrine (decongestant) and chlorpheniramine (anti-histamine) are selected for further discussion primarily due to FDA's access to pediatric PK data of these drugs. Additionally, pseudoephedrine has been implicated in majority of reported deaths in infants and toddlers (Wingert WE et al. 2007).

Pseudoephedrine

Pseudoephedrine is currently in the OTC Final Monograph for oral nasal decongestants for use in adults and children aged ≥2 years of age. Recently, FDA has limited the sale of cold medicines containing pseudoephedrine to behind the counter status, i.e. customers do not have direct access to the product before the sale is made. An additional limit was also placed on the amount that can be purchased on a single day and month. Although, this restricted access was placed because pseudoephedrine is a precursor for the synthesis of methamphetamine, a powerful highly addictive stimulant, it may have an added benefit of reducing access and use by caregivers of infants as well.

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The pharmacokinetic parameters of pseudoephedrine in adults in comparison to children of age groups of 6-11 years and 2-5 years are listed in Table 1 below. Pseudoephedrine is completely and rapidly absorbed from the GI tract with a time to peak concentration (T_{max}) of approximately 2 – 2.5 hours for adults and 1 – 2 hours for children 2 to 12 years of age. It is largely excreted unchanged (55-75%) in urine with an elimination half-life of about 5 – 8 hours. The oral clearance of pseudoephedrine is approximately 26 – 30 L/min. Renal impairment significantly reduces pseudoephedrine clearance.

Following oral administration (per OTC monograph dosing) of 60 mg (adults), 30 mg (6-11 years of age) and 15 mg (2-5 years of age), the rank order of peak plasma concentration (C_{max}) as well as extent of absorption (AUC) was found to be adults > 6-11 years > 2-5 years (Table 1). The body weight normalized clearance estimates for the age groups of 2-5 years and 6-11 years were 0.82 L/h/kg and 0.63 L/h/kg, i.e. 2- and 1.5-fold greater, respectively compared to adults (0.43 L/h/kg). While the terminal elimination half-life remained generally constant across all age groups, the oral clearance (after weight normalization), appears to be higher for younger age groups resulting in approximately 47% and 28% lower pseudoephedrine exposure in age groups of 2-5 years and 6-11 years, respectively relative to adults.

Table 1. Mean (CV%) Pseudoephedrine pharmacokinetic parameters in healthy adults, healthy children (6-11 years) and pediatric allergic rhinitis patients (2-5 years).

PK parameters	Pediatrics (2-5y) (rhinitis patients)	Pediatrics (6-11y) (healthy)	Adults (18-44y) (healthy)
Dose (mg)	15	30	60
N	7	28	25
AUC (ng.hr/mL)	1292 (41)	1735 (27)	2424 (26)
C_{max} (ng/mL)	179 (17)	218 (24)	254 (21)
$T_{1/2}$ (h)	5 (35)	4 (9)	5 (24)
CL/F (L/h)	14 (47)	19 (28)	26 (24)
CL/F (L/h*kg)	0.82	0.63	0.43

Note: Data obtained from Clinical Pharmacology Reviews of NDA 21-373 (Children's Advil Cold Suspension) and NDA 21-374 (Advil Cold Sinus Liquigels)

Chlorpheniramine

Chlorpheniramine is currently in the OTC Final Monograph for antihistamine for use in adults and children aged ≥6 years of age. The pharmacokinetic parameters of chlorpheniramine in adults in comparison to children of 6-11 year age group are listed in Table 2 below. Chlorpheniramine exhibits variable and incomplete bioavailability (25-59%), elimination half-life varies widely (12-43 h) and approximately 72% is bound to plasma proteins (Huang SM et al. 1982, Peets EA et al. 1972). Chlorpheniramine is metabolized primarily by N-demethylation, accounting for approximately 27% of an oral dose, with 18% excreted unchanged in urine. Urinary excretion rates are dependent on

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the pH of urine and urinary flow, with the rate decreasing as the pH rises and urinary flow decreases (Lai et al. 1979, Beckett and Wilkinson 1965, Simons KJ et al. 1984).

In a PK study of 11 children with allergic rhinitis ages 6-16 years, chlorpheniramine exhibited a mean (SD) elimination half-life of 13.1 (6.6) hours, a mean (SD) clearance rate of 0.43 (0.19) L/hr/kg, and a mean apparent volume of distribution of 7.0 (2.8) L/kg (Simons KJ et al. 1984). In another pediatric PK study, following monograph dosing of 4 mg in adults and 2 mg in pediatric allergic rhinitis patients 6-11 years of age, chlorpheniramine exposure (AUC) was about 32% lower in children compared to adults [NDA 21-587 (Children's Advil Allergy Sinus Suspension)]. This was consistent with the reported 58% greater weight-normalized clearance of the drug for children (0.52 L/hr/kg) compared to adults (0.33 L/hr/kg). The mean terminal half-life in children 6-11 years of age is measurably shorter compared to adults (14 vs. 22 hours). These findings point towards lower exposure for chlorpheniramine in young children.

Table 2. Mean (SD) Chlorpheniramine pharmacokinetic parameters in healthy adults and pediatric allergic rhinitis patients (6-11 years).

PK parameters	Pediatrics (6-11y) (rhinitis patients)	Adults (18-44y) (healthy)
Dose (mg)	2	4
N	30	29
Dose (mg/kg)	0.07	0.07
AUC (ng.hr/mL)	131 (52)	194 (76)
C_{max} (ng/mL)	7.3 (4.4)	8 (1.3)
$T_{1/2}$ (h)	14 (4)	22 (6.5)
CL/F (L/h/kg)	0.52	0.33

Note: Data obtained from Clinical Pharmacology Reviews of NDA 21-587 (Children's Advil Allergy Sinus Suspension)

From the PK data presented in Tables 1 and 2 for pseudoephedrine and chlorpheniramine, respectively, it appears that the monograph recommended dosing in children exhibited progressively lower mean systemic exposure of these drugs compared to adults, which is consistent with greater body weight-normalized oral clearance observed in children relative to adults. Therefore, bodyweight based dose adjustment alone may not be enough to produce systemic exposure of these drugs in children comparable to adults. It is evident that larger than monograph recommended doses for different age groups may be needed to produce equivalent systemic exposure in children as in adults.

Factors affecting drug disposition in children

Children may exhibit different drug absorption and disposition compared to adults and the differences are likely to impact drug response. Pediatric patient cannot be considered as a 'little' adult. During child development particularly in the first two years of life, physiological and biochemical processes governing drug absorption, distribution, metabolism and excretion undergo significant maturation (ontogeny). It is long

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recognized that age related developmental and physiological changes exist not only in pediatric population compared to adults but also within pediatric age groups. In addition, environmental (e.g. exposure to other drugs) and dietary factors (e.g. breast-fed vs. formula-fed infants) can affect PK of drugs in young children (Blake et al. 2006).

Absorption of drugs can be affected by gastric pH, gastric emptying time and intestinal transit times (Kearns GL and Reed MD 1989). Gastric pH value is almost neutral at birth but within hours rapidly falls to between pH 1.5 and 3.0, with gastric acid secretions corrected for bodyweight, approaching lower limit of adult values by 3 months of age. This may enhance absorption of acid-labile drugs such as penicillin. Gastric emptying is prolonged until 6 months of age. Intestinal transit time is decreased in children resulting in incomplete absorption of sustained release products.

Drug distribution is often influenced by a number of age-dependent factors such as quantity of body water and fat composition, and the quantity and binding capacity of plasma proteins (Kearns GL and Reed MD 1989). Total body water is increased and percent of body fat is decreased in infants and children. Albumin concentrations normalize to adult levels at 1 year of age and the binding is decreased in infants. The concentration of α_1-acid glycoprotein also increases over the first year of life. The variability with age in these factors can affect drug binding and thus drug distribution. Further, the blood brain barrier in newborn infant is not fully developed and drugs may cross blood brain barrier resulting in CNS toxicity.

Clearance has been recognized as one of the key pharmacokinetic parameters that determines drug exposure and pharmacological response. Total clearance represents both renal and non-renal pathways of drug elimination and is highly variable in pediatric population. Reviewing the entire range of ingredients in widely used cough and cold medications, it is evident that most of these drugs appear to undergo either renal and/or CYP-mediated hepatic elimination (Table 3). Understanding the ontogeny of these elimination pathways in infants and children is critically important in elucidating variability in PK and PD of cough and cold medications, thus can improve pharmacotherapeutic management of pediatric patients.

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Table 3. Clearance pathways of common cough/cold medications.

Cold/Cough Medications	Clearance	Metabolic pathway
Pseudoephedrine ***(decongestant)***	Major: Renal (55-75% excreted unchanged)	Metabolized to Norpseudoephedrine (primary active metabolite)
Guaifenesin ***(expectorant)***	Rapidly hydrolyzed, no unchanged drug in urine; plasma $t_{1/2}$ = 1 hr (IR)	Hydrolysis (CYPs unknown)
Dextromethorphan ***(anti-tussive)***	Hepatic Clearance: 1575±658 mL/min/kg (2D6 EM), 3.9±1.4 mL/min/kg (2D6 PM); $T_{1/2}$ = 3.4h (EM) vs. 29.5h (PM)	Major: DM to DX by CYP2D6 (O-demethylation); Minor: CYPs3A4 and 2B6 (N-demethylation)
Chlorpheniramine ***(anti-histamine)***	Extensive first-pass metabolism (includes gut); Hepatic (27% of oral dose), Renal (18% excretion dependent on urine pH and flow rate: 27% (pH 5) to 0.3% (pH 8)	CYPs 2D6 & 2C19; Causes CYP2D6 inhibition
Diphenhydramine ***(anti-histamine)***	Major: Renal (94%); Clearance: 6.2 ± 1.7 mL/min/kg; $t_{1/2}$ = 2-8 hrs	Metabolized to diphenylmethoxyacetic acid, then conjugated

DM: Dextromethorphan; DX: Dextrorphan; IR: Immediate-release; EM: Extensive Metabolizer; PM: Poor Metabolizer; CYP: Cytochrome P450

Ontogeny of Renal Clearance

Both maturation and growth are involved in the age-associated increase in renal clearance capacity (Alcorn J and McNamara PJ, Part I 2002). The total clearance for renally cleared drugs is generally directly proportional to the body surface area and therefore body weight, provided renal clearance mechanisms are matured to the adult level. They are believed to be immature at birth and this immaturity is thought to persist for several months to several years before they approach weight-normalized adult values. While adjustment of drug pharmacokinetic parameters based on body-weight or body surface area may occasionally account for the differences related to growth, it very seldom can explain the exponential maturation of these clearance processes and hence is unlikely to predict accurate dosing for pediatric patients. Dramatic increases in renal function occur in the postpartum period, and by 18-24 months of age, glomerular filtration rate normalized to bodyweight has approached adult values. The ontogeny of active tubular secretion and tubular reabsorption and their impact on the elimination of drugs remain largely unknown.

There are reports (Alcorn J and McNamara PJ, Part II 2002) in the literature that suggests quantitative methods to normalize renal function in children and predict relative dosing rate in children based on adult estimates. One such report (Hayton WL 2002) proposed an exponential mathematical model that characterized both the maturation and growth of the renal function parameters such as glomerular filtration (GF), active tubular secretion (AS) and renal blood flow (Q_R). The time to adult values (i.e. 90% maturation) are calculated

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to be about 2 years for GF and about 1 year for AS and QR consistent with previous literature. For renally eliminated drugs, the model can potentially be used to estimate pediatric dosing rate that is based on the adult dosing rate and the age and weight of the child. For example, for a drug that is eliminated by glomerular filtration only, a 7-month-old child would have a model-predicted dosing rate (mg/kg) that is about 1.78-fold the mature-adult dosing rate. Pseudoephedrine is predominantly eliminated unchanged in urine. Based on PK data presented in Table 1, pseudoephedrine would require a greater dosing rate in children 2 years and older compared to adults to achieve comparable systemic exposure. For children below the age of 2 years, no PK data is currently available and therefore such determination is not possible in this age range.

Ontogeny of Hepatic Clearance

Hepatobiliary mechanisms such as drug metabolizing pathways and/or hepatic transport may have significant impact on the hepatic clearance of many drugs (Alcorn J and McNamara PJ, Parts I, 2002; Alcorn J and McNamara PJ, Part II, 2002). In general, when compared with adult activity levels normalized to amount of hepatic microsomal protein, hepatic cytochrome P450-mediated metabolism and the phase II reactions of glucuronidation, glutathione conjugation and acetylation are deficient in the neonate, but sulfate conjugation is an efficient pathway at birth. Parturition triggers the dramatic development of most drug metabolizing enzymes, and each enzyme demonstrates an independent rate and pattern of maturation. Large inter-individual variability is associated with the developmental expression of drug metabolizing enzymes making the ontogeny of hepatic metabolism a highly variable process. Cytochrome P450 (CYP) enzymes are a superfamily of enzymes that are responsible for the oxidative metabolism of a wide variety of lipophillic substrates. By the first year of life, most CYP enzymes are believed to have matured to adult activity levels. CYPs 3A4/5 and 2D6 appear to be the two principal enzymes that are widely associated in the metabolism of commonly used cough and cold medications such as dextromethorphan, chlorpheniramine and diphenhydramine that primarily undergo elimination via liver.

CYP3A4

During the transition from fetal to neonatal life the total CYP3A content appears to be relatively stable (de Wildt SN et al. 1999). CYP3A4 is the principal adult liver enzyme; CYP3A5 exhibits low and variable expression in adult liver and CYP3A7 is the fetal form. CYP3A4 mRNA is very low before birth but increases rapidly after the first week of life, reaching 50% of adult levels between 6 and 12 months of age. On the other hand, CYP3A7 activity is high during embryonic and fetal life and decreases rapidly during the first week of life (Figure 2). During infancy, CYP3A4 activity appears to be slightly higher than that of adults in line with literature findings of faster *in vivo* clearance of widely accepted CYP3A4 substrates such as midazolam and tacrolimus in children compared to adults. Therefore, dramatic changes occur in the activity of CYP3A isoforms during childhood that may impact the clinical pharmacokinetics of CYP3A substrates.

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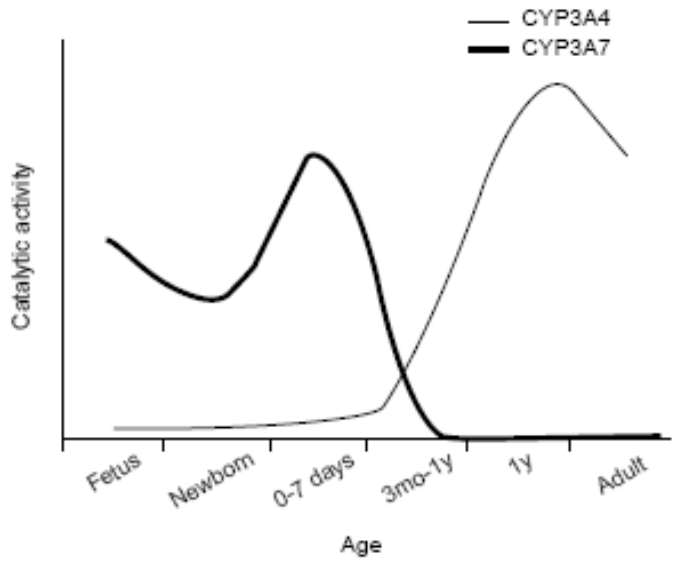

Figure 2. Ontogeny of CYPs 3A4 and 3A7 activity expressed as activity measured using isoform-specific probes in human liver microsomes. *(Adopted from de Wilt et al. 1999)*

CYP2D6

Like CYP3A4, immediately after birth, CYP2D6 protein and enzyme activity begin to increase (Treluyer JM et al. 1991). Limited data exist regarding developmental expression of CYP2D6 after 1 month of age. Large inter-individual variability in CYP2D6 activity is attributed to well-established genetic polymorphism of this enzyme leading to a wide spectrum of phenotypes including poor, intermediate, extensive and ultra-rapid metabolizers. A recent publication from Blake et al. (2007) described the ontogeny of dextromethorphan, a widely recognized CYP2D6 probe substrate and a cough suppressant in the OTC monograph, in the first year of life, which is illustrative of developmental changes in CYP2D6 in vivo expression and activity.

Ontogeny of Dextromethorphan metabolism

Dextromethorphan (DM) undergoes O-demethylation to dextrorphan (DX), a well established index reaction for CYP2D6 activity *in vivo*. In parallel, DM also undergoes N-demethylation to 3-methoxymorphinan (3HM), in humans (Figure 3) reflective of CYP3A activity as well as possibly CYP2B6 activity. CYP2D6 phenotype in adults is commonly expressed as the urinary molar ratio of DM to DX (i.e. DM/DX) while 3-hydroxymorphinan to dextrorphan (3HM/DX) has been shown to correlate well with midazolam clearance in adults, indicating that this ratio may provide a surrogate for CYP3A activity *in vivo*.

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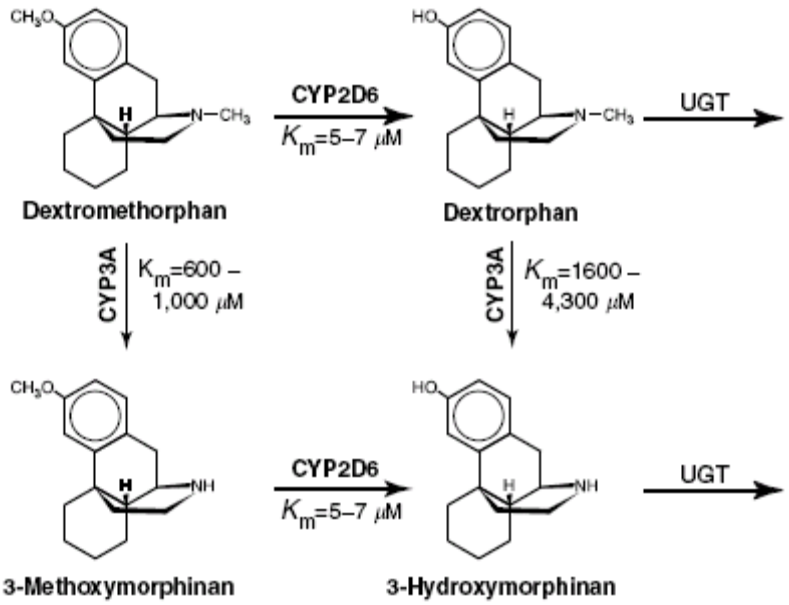

Figure 3. Metabolic pathways of O-demethylation and N-demethylation of Dextromethorphan. *(Adopted from Blake MJ et al. 2007)*

The influence of post-natal age on CYP2D6 activity, as assessed by the DM/DX ratio, is illustrated in Figure 4. This data demonstrates no apparent age-related difference in CYP2D6 activity, as reflected by *in vivo* assessment of the DM/DX urinary molar ratio, from 2 weeks of age through the first year of life although considerable variability in DM/DX ratios was apparent at each time point that can be attributed to individual genotype. These results, however, must be interpreted with caution in the context of a) methodological challenges (such as limitation in the collection of urine volume) to conducting an *in vivo* study in infants and b) a recent publication (Borges et al. 2005) suggesting limited value of DM/DX urinary molar ratio for detecting subtle changes in CYP2D6 activity.

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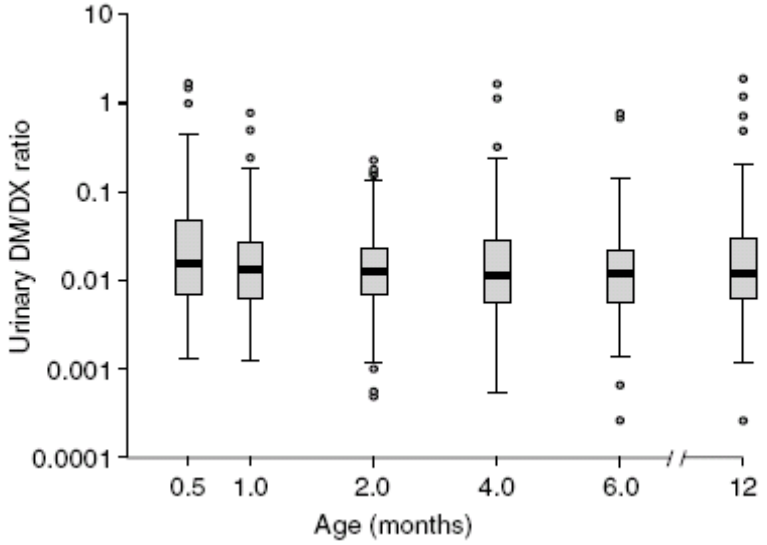

Figure 4. Effect of post-natal age on CYP2D6 activity. Boxes are interquartile range; bars are medians. *(Adopted from Blake MJ et al. 2007)*

In contrast to O-demethylation (indicative of CYP2D6 activity), which appears to be well developed by 2 weeks post-natal age, dextromethorphan N-demethylation activity increases slowly after birth becoming a predominant urinary metabolite at 6 months of age and beyond (Figure 5). Conversely, the fractional recovery of DX was found to decrease from over 70% at 2 weeks to approximately 30% at 1 year. This increase in 3HM at the expense of DX over the first year of life indicates a metabolic shift from primary dextromethorphan metabolism of O-demethylation by CYP2D6 to N-demethylation by CYP3A4 and/or CYP2B6. This apparent shift may reflect the development changes and expression of CYP enzymes in the liver and/or the intestine.

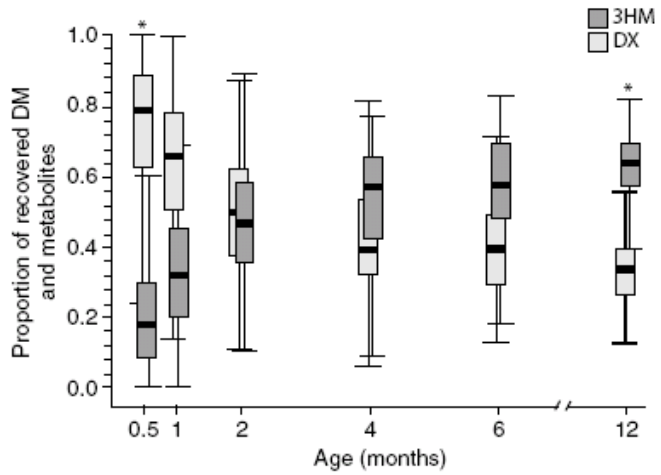

Figure 5. Change in the fractional molar recovery of DX and 3HM in urine with age in the first year of life *(Adopted from Blake MJ et al. 2007)*

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Current practice to achieve optimal pediatric dosing

Through many legislative initiatives, including the Food and Drug Administration Modernization Act (FDAMA) in 1997, the Best Pharmaceuticals for Children Act (BPCA) in 2002 and The Pediatric Research Equity Act (PREA) in 2003, FDA has mandated the requirements for pediatric studies of certain drugs and biologics that have resulted in improvements in pediatric information in the labeling such as proper dosing and identification of the risks of therapies in young patients (Roberts R et al. 2003). These changes revealed that pediatric dosing may not be always obtained by simply applying weight based calculations to the adult dose. These studies highlight the importance of obtaining PK data within an appropriate study design to arrive at optimal dosing in children.

A recent example of unique pediatric dosing recommendation down to 2 months of age based on PK data in children for an antibacterial combination prescription product of piperacillin/tazobactam (Zosyn®) illustrates the utility for appropriately designed PK studies in the target pediatric population. Tornoe et al. (2007) conducted a comprehensive pharmacometric analysis that identified clearance to be dependent on both body weight and age in pediatric patients ≤2 years, which is consistent with the expectation based on maturation of renal function by 2 years of age. To account for the age factor influencing the systemic clearance of piperacillin in patients less than 2 years of age, the pediatric dosage was recommended to be reduced by a factor that depends upon age, as shown in Figure 6. With the assurance of adequate safety down to 2 months of age, the population PK analysis and simulations have been used to obtain the following age-specific stratified dosing recommendations (reference: Zosyn® Label) based on achieving exposures similar to adults: for pediatric patients ≥9 months, a dose of 100/12.5 mg/kg every 8 h and for pediatric patients aged 2-9 months, the dose of 100/12.5 mg/kg should be reduced by a factor of 0.8. Although this example pertains to a prescription medication that will be administered under the supervision of a healthcare provider, the concept can also be applied to OTC products to arrive at age-stratified dosing determinations in children.

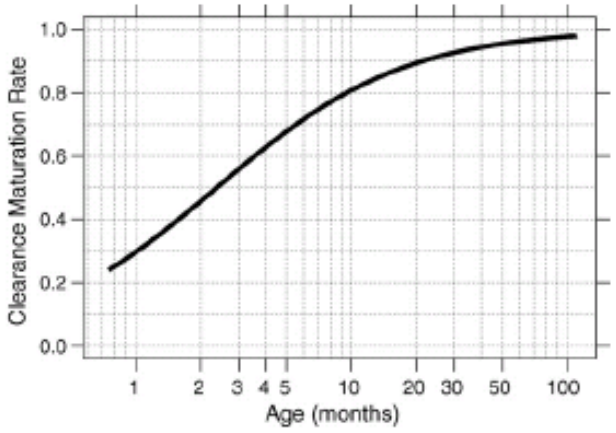

Figure 6. Maturation rate of piperacillin clearance (CL) in pediatric patients after accounting for body weight differences. Clearance in patients ≥2 years is similar to that in adults after adjustment for body weight. *(Adopted from Tornoe et al. 2007)*

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Post-mortem drug redistribution

Excessive post-mortem levels of cough and cold medications in recent reports of deaths in young children could not be easily explained by common causes of drug overdose and drug interaction. The phenomenon of drug redistribution following death has been considered as a contributing factor for such high post-mortem levels (Cook DS et al. 2000). Various factors such as the site of postmortem blood collection, timing of collection after death, type of biological matrix, sample processing influence the measurement of post-mortem drug concentration (Leikin JB and Watson WA 2003). Several common OTC cold and cough drugs have been found to undergo postmortem redistribution, therefore, likely to have some contribution towards such high levels of these drugs in post-mortem blood samples in children.

Recent reports of deaths and other serious adverse events associated with the use of over-the-counter (OTC) cough and cold products in young children have documented very high post-mortem concentrations of these drugs (Gunn VL et al. 2001; Wingert WE et al. 2007; Boland DM et al. 2003; Marinetti L et al. 2005). Post-mortem drug analysis is at the heart of forensic toxicology to explain chemical use in the immediate antemortem setting and role of chemical toxicity in the cause of death. Therefore, it is important to highlight some of the key factors that can influence the interpretation of post-mortem analysis in order to predict accurately the antemortem chemical cause of death and understand the science of the change in drug concentration over time after death also known as drug re-distribution. Some of these factors determining drug redistribution may be pertinent to post-mortem findings relevant to this discussion.

There is often an incorrect assumption that death results in a total cessation of all activity and therefore the post-mortem blood drug level is an accurate representation of ante-mortem blood drug concentration. This concept fails to consider the dynamics of drug distribution and transformation that occur in the perimortem and postmortem state and therefore can potentially lead to erroneous conclusions about the cause of death. The extent and kinetics of post-mortem changes are dependent upon the chemical characteristics of the drug, primarily due to passive diffusion of the drug as the tissue integrity is lost, fluid shifts, drug's pKa and apparent volume of distribution, and the condition of the body ((Leikin JB and Watson WA 2003). Two important variables that affect postmortem drug concentrations include anatomic blood collection site and postmortem sampling time. The cardiac to peripheral blood level (C:P) ratio of drug levels in postmortem blood samples has been evaluated as a measure of the potential for postmortem drug redistribution. Drugs that have high ratios are believed to have greater potential for redistribution. In these circumstances, collection of autopsy samples from either a heart chamber or the pericardial sac may result in measurement of a drug concentration that is significantly higher than the peripheral concentrations, resulting in inaccurate interpretation of the results. Among many factors, the drug's apparent volume of distribution is recognized as an important determinant of postmortem redistribution. Drugs that have a relatively large apparent volume of distribution (greater than 3 L/kg) are candidates for redistribution from tissue into vascular space via passive diffusion from surrounding tissue and extra vascular fluid. Leikin and Watson (2003) reported that

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several common OTC cough and cold drugs have been found to undergo postmortem redistribution (Table 4). Therefore, post-mortem redistribution may have some contribution towards reported high levels of these drugs in post-mortem blood samples in young children. In addition, whole blood is the primary matrix for quantitative autopsy analysis whereas plasma/serum is the usual matrix used in clinical settings. This difference in matrix collection potentially can also lead to inaccurate post-mortem analysis in some cases. Additionally, depending on the time after death that the sample is collected, the consistency of the blood sample and thereby analysis changes with clotting, fluid movement, and cellular components.

Table 4. List of cough/cold medications in which post-mortem redistribution may occur.

Drugs	C:P ratio*
Pseudoephedrine	1.5
Dextromethorphan	2.0
Diphenhydramine	2.3
Chlorpheniramine	3.1

*C:P ratio = cardiac blood : peripheral blood ratio
Reference: Leikin and Watson (2003)

Conclusions

Following FDA's decade long pediatric initiatives, improvements in pediatric information in the drug labeling have been achieved for a number of prescription medications across various therapeutic areas as a result of targeted PK/safety studies to determine optimal dosing and safety in pediatric patients.

These studies highlight the following points:

- created unique opportunities to recommend critical labeling changes that include unique pediatric dosing capturing the effects of growth and maturational changes in children during infancy;
- provided evidence that pediatric dosing can not be always obtained by simply applying weight or surface area based calculations to the adult dose;
- highlighted the importance of evaluating drug clearance in pediatric population that often impact drug exposure in children, which ultimately determine efficacy and safety;
- revealed that drug clearance is a highly variable parameter in the pediatric population;
- exhibited clearance estimates in children that were not always predictable based on prior adult information for many drugs. They were either lower or higher and in some instances, comparable to adult values. Some of these could be explained by body-

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weight related differences, others related to body surface area and large number of them could be mechanistically explained by differences in maturation of drug metabolizing enzymes and/or organs of elimination.

Robust and well-designed clinical PK/safety trials in children are currently lacking in the area of cough and cold medications. Provided the assumptions of similar disease progression and similar response to pharmacologic intervention between pediatric and adult population are true, carefully designed pediatric PK trials could be very informative in an effort to optimize dosing in children of different ages. These studies should, at a minimum, attempt to obtain pharmacokinetic data in various age groups, especially in children 2 years and younger with limited blood sampling strategy in order to propose dosing recommendations based on modeling and simulation techniques similar to that demonstrated with Zosyn®. If the disease progression is different between adults and children, then therapeutic response may also be different and in that case, efficacy and safety studies may be needed to determine appropriate dosing in children.

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BACKGROUND INFORMATION FOR ADVISORY COMMITTEE MEETING

Date:	September 11, 2007
To:	Members, Non-Prescription Drugs Advisory Committee
From:	Peter Starke, MD Associate Director for Safety Division of Pulmonary and Allergy Products (DPAP)
	Charles E. Lee, MD Medical Team Leader Division of Pulmonary and Allergy Products (DPAP)
Subject:	Considerations for extrapolation of efficacy from adults to children: Examples and experience from the Division of Pulmonary and Allergy Products

The Division of Pulmonary and Allergy Products is asked provide background information to support your deliberation regarding on the efficacy of antihistamines, decongestants, and cough medicines for the treatment of cough and cold in children, and to provide information regarding our experience with the use of extrapolation of efficacy from adults to support indications in children. We have limited experience with applications for these products for cough or cold indications, although we do a good deal of experience with similar products for other respiratory indications in children. We will present the considerations we use to evaluate new pediatric applications, including how we decide whether extrapolation of efficacy from adults to children may be appropriate. We will discuss the information needed for pediatric applications, including applications that use extrapolation from adult data. We will provide several examples of development programs for pediatric respiratory indications, which may be of use in your deliberations.

We will discuss the 1994 Pediatric Rule that mandated pediatric use information in the labeling, and allowed for extrapolation of efficacy from adults to children "when the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in pediatric and adult populations." That Rule is now embodied in the Pediatric Research Equity Act, called PREA. PREA, which amends the Food Drug and Cosmetic Act and was signed into law on December 3, 2003, applies to all drug and biologic applications submitted on or after April 1, 1999. It requires submission of pediatric assessments (birth to 16 years) at the time of submission of drug and biologic applications (unless waived or deferred) if the disease occurs in both adult and pediatric populations. Although PREA does not apply to monographed drugs, the information is helpful in understanding the considerations we use to decide on the appropriateness to extrapolate from efficacy data in adults. The decision regarding extrapolation depends upon considerations of the course and pathophysiology of disease, the lower bounds of disease process, immune maturation and response, anatomical differences, and the response to drug. Other factors we use include our experience with the disease and the drug/drug class, systemic versus local activity and exposure, and an estimation of the efficacy/safety balance.

We will touch on the types of studies and endpoints we use for various relevant drugs and indications, and explain the differences between pediatric development programs for systemically active drugs and locally active drugs. We will also discuss types of efficacy data that we require, both subjective and objective, to support pediatric applications. We will discuss the lower age bounds of some diseases that are studied in our division. It is important to note that we have not made any determination regarding the appropriateness of extrapolation for upper respiratory viral illness including cough or colds, although endpoints have been discussed at previous Advisory Committees (in 1994 and 1995) and we have one example of an antihistamine that was studied in adults and adolescents for a cold indication. We will briefly present data from that example, although it should be noted that this example is not an example of extrapolation to children, but rather, an example of the type of data one might expect for a cold indication.

Considerations for Extrapolation of Efficacy from Adults to Children

Examples and Experience from the Division of Pulmonary and Allergy Products

Peter R. Starke, MD
Associate Director for Safety

Charles E. Lee, M.D.
Medical Team Leader

Division of Pulmonary and Allergy Products

Food and Drug Administration
Division of Pulmonary and Allergy Drug Products

Overview

- Pediatric Use Information requirement – Pediatric Rules and Pediatric Research Equity Act (PREA)
- Pediatric drug development for NEW products in the Division of Pulmonary and Allergy Products (DPAP)
  - Decision tree regarding extrapolation
  - Efficacy assessments
  - Examples
    - Allegra – allergic rhinitis and chronic idiopathic urticaria
    - Pulmicort Respules – asthma
    - Tavist – colds

Pediatric Use Information under the Pediatric Research Equity Act (PREA)

- Original "Pediatric Rules"
  - 1994 Pediatric Rule (pediatric use information and extrapolation of efficacy)
  - 1998 Pediatric Rule (pediatric study requirement)
- PREA (December 3, 2003)
  - Amends the FD&C Act to add Section 505B (21 CFR 314.55)
  - Requires submission of pediatric assessments (birth to 16 years) at the time of submission of drug and biologic applications submitted on or after April 1, 1999, if the disease occurs in both adult and pediatric populations
  - Pediatric assessments may be waived or deferred
  - Requires assessments using appropriate pediatric formulations
  - Does not apply to monographed drugs

Pediatric Research Equity Act (PREA)

- Triggered by an application with a new:
  - Active ingredient
  - Indication
  - Dosage form
  - Dosing regimen
  - Route of administration

- Works in conjunction with the Best Pharmaceuticals for Children Act (BPCA, 1/4/02), which provides for 6 months of marketing exclusivity ("the carrot") for studies performed in response to a pediatric Written Request

Substantial Evidence under PREA*

- "Substantial evidence" may be supported by adequate and well-controlled studies in adults, supplemented by dosing, PK, and safety data in the appropriate pediatric age groups, IF:

  "The course of the disease and the effects of the drug [both beneficial and adverse] are sufficiently similar in pediatric and adult populations"
- "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group"
- If extrapolation of effectiveness is inappropriate, pediatric efficacy studies may be required

* Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, September 2005; http://www.fda.gov/cder/guidance/

Extrapolation of Efficacy to Children

- Depends upon
  - Course and pathophysiology of disease / lower bounds of disease process
  - Immune maturation and response
  - Anatomical differences
  - Response to drug
- Other factors
  - Experience with the disease and drug / drug class
  - Systemic vs local activity and exposure
  - Estimation of the efficacy / safety balance

Difficulties with Performing Studies in Children

- Consent / assent
- Ethics
- Limitations of blood draws
- Subjective endpoints
- Objective endpoints

Lower Age Bounds of the Disease

- Taking all the scientific information (course of disease, etc.) into account, DPAP considers the following to be the lower age bounds of some diseases to be studied:
  - Allergic rhinitis
    - Seasonal (SAR) – 2 years
    - Perennial (PAR) – 6 months
  - Chronic idiopathic urticaria (CIU) – 6 months
  - Asthma – 6 months

Systemic vs Locally Acting Drugs

- Systemic drugs
  - Drug measurable in blood
  - Blood is relevant biospace
  - PK allows estimation of dose from adult data
  - Examples: Oral drug products
- Locally active drugs
  - Drug may be measurable in blood, but
  - Blood is not relevant biospace (relevant biospace is lung or nose)
  - PK not helpful for estimation of dose
  - Examples: Intranasal and orally inhaled drugs

Allergic Rhinitis Efficacy Assessments*

- Total Nasal Symptom Scores
  - Rhinorrhea, nasal congestion, nasal itching, sneezing
  - Severity rated on 4-point scale, 0-3
- Patient-assessed
  - Over 2 weeks for SAR
  - Over 4 weeks for PAR
- Reflective and instantaneous scoring recorded in a diary at least as often as the dosing interval

* Draft Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products, June 2000; http://www.fda.gov/cder/guidance/

Asthma Efficacy Assessments

- FEV_1 – assessed differently for reliever and controller drugs
- PEF, AM and PM
- Symptom scores – used in Pulmicort Respules NDA
- Pre-defined asthma worsening criteria (exacerbations)

Systemic vs Locally Acting Drugs

- Systemic drugs
  - Drug measurable in blood
  - Blood is relevant biospace
  - PK allows estimation of dose from adult data
  - Examples: Oral drug products
- Locally active drugs
  - Drug may be measurable in blood, but
  - Blood is not relevant biospace (relevant biospace is lung or nose)
  - PK not helpful for estimation of dose
  - Examples: Intranasal and orally inhaled drugs

Pediatric Development Programs – Systemic drugs

- Efficacy and safety usually established in adults and adolescents first
- Determine whether the course, pathophysiology, and drug's effect are substantially similar between children and adults
- Different efficacy approaches in successively younger age groups depending upon ease of obtaining a cooperative response
  - Efficacy endpoints evaluated in patients as young as can cooperate
- PK in all ages
- Safety in all ages

Allegra (fexofenadine HCl), Pediatric patients

- Approved in 1996 for SAR in patients ≥12 years of age at a dose of 60 mg twice daily

SAR, 6-11 years (30 mg BID)

- PK – comparable exposure to adults
- Efficacy and Safety: 2 randomized, double-blind, placebo-controlled, 2-week SAR studies

SAR, 2-5 years (30 mg BID)

- Extrapolation of efficacy based on 3 PK and 3 Safety studies in children with allergic rhinitis 6 months through 5 years

CIU, 6 months - 11 years (15 and 30 mg BID)

- Extrapolation of efficacy demonstrated in three 4-week CIU studies in patients ≥12 years
- PK and Safety in all ages

Pediatric Development Programs – Locally active drugs

- Efficacy and safety usually established in adults first
- Efficacy endpoints evaluated in patients as young as can cooperate AND by caregiver scoring
- Local and Systemic safety in all ages
- Asthma example:
  - Ages 4-6 through 11 years
    - Efficacy (FEV_1, PEF, symptom scores)
  - Age 4-6 years and below
    - Efficacy – Caregiver symptom scores
  - All ages: Safety, PK, and appropriate systemic safety studies (HPA axis, growth, etc.)

Pulmicort Respules (budesonide nebulization suspension)

Pulmicort Turbuhaler

- Approved in 1997 for maintenance treatment of asthma in ages 6 years and older

Pulmicort Respules

- Approved for patients 12 months to 8 years of age based on 3 randomized, double-blind, placebo-controlled, parallel group 12-week studies in 1018 pediatric patients 6 months to 8 years of age with a variety of disease severity, and previously on or off ICS
- Doses studied: 0.25, 0.5, 1 mg once or twice daily
- Efficacy endpoints:
  - Co-primary: Nighttime and daytime asthma symptom scores (0-3 scale) in all patients
  - Supported by: FEV1, PEF in older subgroup

Tavist-1 (clemastine fumarate, 1.34 mg)

- Clemastine fumarate
  - Antihistamine of the ethanolamine class (structurally similar to diphenhydramine and carbinoxamine)
  - Anticholinergic activity
- Rx to OTC switch approved in 1992 for allergic rhinitis
- Rx supplement approved in 1996 for treatment of colds in patients ≥12 years of age

Tavist-1, Colds, ≥12 years

- Program included: 1 natural and 1 induced cold study
- Additional information from 4 natural cold marketing studies not performed under the IND
- Subject of a joint Pulmonary-Allergy and Nonprescription AC meeting, November 1995
- AC Recommended approval for the treatment of rhinorrhea and sneezing in adults and children 12 years of age and older with the common cold

Natural cold study

- Randomized, double-blind in 403 previously enrolled patients, treated with Tavist-1 or placebo for 5 days within 24 hours of the start of cold symptoms
- 1° efficacy endpoint: Change from Day 1 (baseline – instantaneous) to Day 2 and 3 (retrospective 24-hour) scores for sneezing and rhinorrhea, 0-4 scale

Natural cold study

Treatment group means, 2-way ANOVA, ITT population

Day	Tavist-1	Placebo	Diff	p-value
Sneeze				
1 (baseline)	1.17	1.32	0.15	0.077
2	0.74	1.16	0.42	<0.001
3	0.54	0.90	0.36	0.001
4	0.31	0.70	0.39	<0.001
Rhinorrhea				
1 (baseline)	1.73	1.65	-0.08	0.419
2	1.46	1.58	0.12	0.179
3	1.02	1.39	0.37	<0.001
4	0.76	1.10	0.34	<0.001

Summary

- Pediatric Use (PREA) requirements and extrapolation of efficacy
- Application to efficacy for NEW products in the Division of Pulmonary and Allergy Products (decision tree)
  - Course and pathophysiology of disease
  - Immune maturation and response
  - Anatomical differences
  - Response to drug
  - Systemic vs local activity and exposure
  - Experience with the disease and drug / drug class
  - Estimation of efficacy / safety balance
- Efficacy assessments
- Examples to illustrate relevant drugs, indications, and pediatric development programs

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Date:	September 14, 2007
To:	Susan Johnson, Pharm D, PhD, Acting Director Division of Nonprescription Regulatory Development
Thru:	Kellie Taylor, Pharm D, MPH, Acting Team Leader 9/14/07 Carol Holquist, R.Ph., Director Division of Medication Errors and Technical Support, HFD-420
From:	Richard Abate, R.Ph, MS, Safety Evaluator Division of Medication Errors and Technical Support (DMETS), HFD-420
Subject:	**Postmarketing Safety Review of Medication Errors Involving Over-the-Counter Cough and Cold Products in Pediatric Patients (Newborn to Five Years)**
Drug Name(s):	Brompheniramine, Chlorpheniramine, Dextromethorphan, Diphenhydramine, Guaifenesin, Phenylephrine and Pseudoephendrine.
Applicant/sponsor:	Multiple
OSE RCM #:	2007-1445

CONTENTS

EXECUTIVE SUMMARY

DMETS identified and evaluated medication error cases involving Over-the-Counter (OTC) cough and cold products given to pediatric patients under the age of six years in preparation for an Advisory Committee Meeting. A total of 36 medication errors were identified in FDA's Adverse Event Reporting System (AERS). Most of the cases (n=25) involved combination or multi-ingredient cough and cold products rather than single-ingredient products. The errors occurred with many different product lines; and no single product line had a significantly greater number of errors than any other. The majority of the error types identified involved improper dosing. Following review of the medication error cases in AERS and parent discussions from the Internet we determined the contributing factors or root causes for these errors include concurrent administration of products with the same ingredients or similar thereaptutic class, difficulty in determining the dosing of these products, problems associated with dosing devices and product line or name confusion. Our findings support the petitioner's view that these products are prone to unintentional overdose. DMETS recommends standardization of dosing devices, considering standardizing the concentrations of active ingredients, studies in pediatric patients to better define dosing in this population, and elimination of multi-symptom pediatric cough and cold products. These recommendations will minimize dosing errors in this patient population. See Section 6 for a complete list of these recommendations.

1 BACKGROUND

The Baltimore City Health Department submitted a Citizen's Petition to the FDA on March 1, 2007 expressing concerns about the safety and efficacy of the use of Over-the-Counter cough and cold products in children under six years of age., The Citizen's Petition provided examples of specific medication errors including overdose of these Over-the-Counter medications in this pediatric age group. The Petitioners' requested that FDA take action on the labeling of the products because the products are prone to unintentional overdose and have not been shown to be safe and effective in children less than six years of age. In response to this Citizen's Petition, the Office on Non-Prescription Drugs scheduled an Advisory Committee Meeting in October 2007 to discuss the data regarding the safety and efficacy of these products in this age group.

1.1 INTRODUCTION

This postmarketing safety review of medication errors is in response to a request from the Division of Nonprescription Regulatory Development (ONP) to identify medication error cases from the Adverse Events Reporting System (AERS) involving pediatric patients under the age of six years given Over-the-Counter cough and cold products in preparation for the October 2007 Advisory Committee Meeting on this subject.

1.2 PRODUCT LABELING

DMETS reviewed the product labels and labeling contained in Appendix 1. This Appendix lists the product names identified in the medication error cases reviewed, the current active ingredients contained in each of these products, and whether Drug Facts includes labeled dosing for specific age groups (i.e., less than two years, two to five years, and six to twelve years.) In certain cases, DMETS was unable to determine what specific product was involved because the narratives referred to product(s) involved only by their active ingredients.

The Citizen's Petition noted that OTC cough and cold product names may contain the word "infant" or "baby" and that the labels contain images of children under the age of six.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

This postmarketing safety review was conducted to evaluate the medication errors involving Over-the-Counter (OTC) cough and cold products in pediatric patients less than six years of age. The search criteria were chosen based on the issues raised in the Citizen's Petition and the focus of the upcoming Advisory Committee Meeting.

The Division of Drug Risk Evaluation (DDRE) within the Office of Surveillance and Epidemiology (OSE) is reviewing serious adverse events related to the active ingredients Pseudoephedrine, Chlorpheniramine, Dextromethorphan, and Diphenhydramine (OSE # 2007-1022, DDRE). DMETS initially evaluated the cases used for that review to identify medication error cases contributing to serious adverse events. This case series included events from 2002 forward for the medications Chlorpheniramine, Pseudoephedrine, Dextromethorphan and Diphenhydramine. As the number of medication errors identified in these series was limited, DMETS completed an additional search of the AERS database and requested searches of the Institute of Safe Medication Practices databases to identify additional medication errors cases involving commonly used OTC cough and cold products.

Since the OTC cough and cold products utilized for pediatric patients include products containing medications other than the aforementioned four drugs, DMETS expanded our search to include other medications in CFR 21.341, specifically guaifenesin and phenylephrine, for the sake of completeness. For the purposes of this review, cough and cold products will be referred to as those products containing the aforementioned active ingredients.

Finally, to identify causes of medication errors related to the use of OTC cough and cold medications that are not captured through traditional reporting programs, DMETS searched Internet websites for discussions from parents sharing their experiences using these products.

2.2 AERS SELECTION OF CASES

DMETS searched the FDA Adverse Event Reporting System (AERS) using the active ingredient terms, "Brompheniramine," "Chlorpheniramine," Dextromethorphan," "Diphenhydramine," "Guaifenesin," "Phenylephrine," and "Pseudoephedrine" and the verbatim terms "Dimet%," Robitus%," "Sudafed%," "Chlortrime%," "Benad%," "Dextrometh%," "Pseudoephed%," " Chlorphen%," "Diphenhyd%," " Brompheni%," "Guaifen%," "Tussin%," Guaitus%," "Neosyn%," and "Phenylep%," as well as the MedDRA terms "medication errors" (HLGT) and "pharmaceutical product complaint" (PT). In addition, the search criteria was limited to patients whose age fell between zero to six years. DMETS placed no limits on the dates when these reports were identified.

Additionally, DMETS excluded cases from this review that involved the following: accidental ingestion of a product by a child, intentional or malicious overdose by the caregiver, and errors involving prescription cough and cold medications solely. In addition, DMETS excluded cases that did not provide details on the source of the dose the parent or caregiver elected to use for their child when the product is not labeled for use in their child's age group since we could not determine if this use was consistent with a prescriber's recommendation or representative of a medication error.

2.3 INTERNET SEARCH

DMETS searched the following websites for patient and/or caregiver discussions of over-the-counter cough and cold products to identify behaviors parents have when using these products: www.epionons.com, www.amazon.com, and www.drugstore.com.

2.4 ISMP DATABASES

DMETS requested the Institute of Safe Mediation Practices (ISMP) search the USP-ISMP Medication Error Reporting Program (MERP) database, Pennsylvania Patient Safety Reporting Program database, and retail pharmacy medication error databases for errors involving Over-the Counter cough and cold products and children under the age of 6 years.

3 RESULTS

3.1 MEDICATION ERRORS CASES (AERS)

In total 36 medication error cases (n=36) were retrieved involving over-the-counter cough and cold products in children five years of age and under.

The types of errors identified include the following: twenty-six cases (n=26) of improper dose - resulting in overdose, under dose or extra dose, three cases (n=3) of the use of the wrong drug, three cases (n=3) of a dose given at the wrong time or frequency, two cases (n=2) of medication given via the wrong route of administration, one case (n=1) of the patient receiving duplicate therapy (the same class of drug but not the same drug), and finally, one case (n=1) of the using the wrong strength or concentration of the medication. Appendix 2 contains a summary of these cases.

Most of the cases (n=25) involved combination or multi-ingredient cough and cold products rather than single-ingredient products. The errors occurred with many different product lines; and no single product line had a significantly greater number of errors than any other.

The Drug Facts labeling was published in 1999 with full compliance expected by May 16, 2003. However, more than half of the medication errors cases identified in AERS occurred in the past four years, after the expected compliance to Drug Facts labeling (n=20). Nine cases occurred after 2000 but before the Drug Facts changes were enacted; and seven of the cases occurred prior to the year 2000.

Twenty-two (n=22) cases involved children under the age of two years. Most of these cases (n=17) occurred after the Drug Facts labeling was fully in place.

These medication errors typically occurred in the household setting (n=34), except for two (n=2) which occurred in the inpatient setting. Of those cases that occurred in the household setting, fourteen medications error cases (n=14) occurred after the parent sought the advice of a healthcare provider.

3.1.1 Outcomes

Of the 36 cases (n=36) cases identified in AERS, nine cases (n=9) resulted in death according to the detail contained in the case narratives. The child was under two years of age in seven of the nine cases of death. In eight of these cases (n=8), the death was the result of an overdose of medication based on the detail included concerning the toxic levels of medication in the child's system. The remaining death (n=1) involved a 3 month old who died of pneumonia, but the infant had elevated levels of pseudoephedrine in her system per the case report. DMETS notes that one

of the cases involving children under two occurred in Canada, thus factors contributing to the error could be unique to the Canadian product's labeling.

Ten cases (n=10) required the child be evaluated by a healthcare provider either in the emergency room (n=8) or evaluated in their pediatrician's office or by consultation over the telephone.

The remaining seventeen cases reported resolution of any reaction following discontinuation of the medication or no outcome was reported at all.

3.1.2 Contributing Factors/Root Causes

Some of the case narratives describe factors that contributed to the medication errors. These factors include the use of concurrent therapy with the same active ingredient or product class in seven cases (n=7), dosing errors in six cases (n=6), problems encountered with the calibrations on the dosing device or some issue with the use of the use of the device itself in four cases (n=4), product line or name confusion issues in two cases (n=2), using medication purchased for an older sibling in two cases (n=2), and formulation changes in one case (n=1). Appendix 2 lists the factors contributing to each error .

3.2 INTERNET SEARCH

The Internet website www.epinions.com provided comments from parents and caregivers concerning their experiences with the use of OTC cough and cold products. These comments could be categorized into the following four themes: difficulty determining the dose from the labeling, difficulty selecting the correct product from the variety of products available in the marketplace and the impact on choosing the right product, problems associated with measuring devices and product packaging, and how prescribers give dosing directions. DMETS believes that these discussions describe some of the typical factors that contribute to medication errors with cough and cold products. A complete listing of these comments can be found in Appendix 3. DMETS identified no discussions describing the use of OTC cough and cold products on www.amazon.com, and www.drugstore.com. Thus, these Internet locations did not provide any additional insight to contributing factors to error.

3.3 ISMP DATABASES

The Institute of Safe Medication Practices (ISMP) identified no reports in its databases involving OTC cough and cold products in children under the age of six years. However, it is important to note that the USP-MERP, PAPSRS, and retail pharmacy reporting programs generally receive few reports involving Over-the-Counter products because patients and caregivers do not report errors with these products.

4 DISCUSSION

This review was generated in response to a Citizen's Petition concerning the safe and efficacious use of Over-the-Counter (OTC) cough and cold products in children under 6 years of age. Therefore, DMETS has focused the discussion to highlight the medication error risks most relevant to the use of cough and cold product use in this population.

In total DMETS identified 36 cases pertaining to medication errors involving OTC cough and cold products in children less than six years of age. Given the number of cough and cold products available in the marketplace, this number may seem low. However, external experts in medication error reporting state that errors with OTC products are under-reported (Personal Communication with Director of Medication Error Reporting Programs, ISMP; 07/13/2007). This finding is consistent with FDA's experience with medication errors in general and is further

magnified with the OTC status of products. This phenomenon may occur for a number of reasons. First, consumers and caregivers may not realize an error has occurred, or may not know where to report an error to unless significant harm has occurred. This is evidenced by the type of errors we have received where consumers do not realize an error has occurred but an adverse event has resulted from the use of a product. In addition, manufacturers who receive medication error reports or complaints about monograph OTC products may not share this information with the Agency unless a serious adverse event occurred. For these reasons the limited number of cases should be viewed as evidence of how infrequently errors involving OTC products are reported, rather than how frequently errors occur with these products.

4.1 Concurrent Administration of Cough and Cold Products

One of the most common causes of the medication errors reported was the concurrent administration of more than one product containing the same active ingredient or ingredients in the same therapeutic class. Typically, these errors involved the concurrent use of multi-ingredient products. The opportunity for this type of error with Over-the-Counter cough and cold products is tremendous as over 80% of cough cold products contain more than one active ingredient. (OSE # 2007-1022, DCRCS, dated August 9, 2007)

Several overdoses resulted when the parent's or caregiver's used additional OTC therapies to treat the child's symptoms after the physician had already prescribed either prescription or OTC medication for the same child (ISR #'s 4678862-2 and 4883158-X). The parents elected to use additional OTC medications to treat their child's symptoms but failed to realize that the product contained similar or the same active ingredients the child was already receiving in another product. While the Drug Facts labeling may state to "ask your physician or pharmacist prior to the use of" specific classes of medications, parents may not be aware if any OTC cough and cold products fall into these classes of medication. Thus, parents failed to communicate with their children's healthcare providers before using the products concurrently with the prescribed or the parent/caregiver preferred cold product.

In addition, DMETS believes parents may not be fully reading or understanding the labels of cough and cold products when determining whether a product contains the same or a similar ingredient as the product they are currently using. Although 21 CFR 201.66 requires the purpose of each active ingredient appear along with it in the Drug Facts labeling, the labels of these products list the symptoms relieved separately and generally more prominently than the active ingredient/purpose listed below the proprietary name. Parents may read the larger text describing symptoms relieved rather than the ingredients in the product when selecting a medication for their child which is likely to contribute to the confusion. However, the manner in which the sponsor chooses to display the symptoms on the primary display panel of monograph OTC products falls outside the regulatory authority of the Food and Drug Administration.

4.2 Dosing Cough and Cold Products

Many of the OTC cough and cold products sold in United States are liquid formulations that require parents and/or caregivers to measure doses appropriate for their children. As such, the design of the dosing device or lack of a dosing device contributes to dosing errors with cough and cold products.

Some manufacturers provide dosing devices with their oral liquid formulations. However, if the device is incongruent with the dosing instructions on the label and/or is not in alignment with the dosing instructions provided to the caregiver by their prescriber or not the product the prescriber intended the patient to purchase, the device may contribute to the dosing error. For example, Dimetapp Toddler (formerly Infant) Drops, a product described as "drops," contains an accurate

dosing device which is a 1.6 mL oral syringe. However, if the prescriber expects the product to contain a dropper and provides direction for use based on this expectation, then the caregiver is likely to become confused when presented with an oral syringe. In one medication error case (ISR # 4363124-3), a parent mistook the Dimetapp 1.6 mL syringe as the 0.8 mL dropper described by the child's physician which resulted in a two-fold overdose. DMETS believes providing consistent dosing devices that correspond to the dosage formulation (drops vs. liquid) in OTC cough and cold oral liquids may reduce the potential for medication errors.

Some cough and cold products, such as Delsym, do not include a dosing device in the packaging which can also lead to doing errors. This lack of dosing device leads parents to find other means of measuring a dose. One parent improvised and used the cap from the medication bottle rather than a calibrated dosing device to administer the product to their three year old child, which resulted in the patient receiving two to three times the necessary dose (ISR # 3003218-8). In addition, parents attempt to measure accurate doses for their children with any available dosing device in the home, including dosing cups from other OTC products. Because dosing devices for other OTC products may use units of measure that are inconsistent with the cough cold product that parents are trying to dose (e.g., marked in Tablespoons not teaspoons), this can be overlooked by the caregiver and lead to over- or under doses of the medication. In one case, a parent dosed an OTC cold product using a dosing device from a different unspecified product (ISR # 4168717-4). Although there was no outcome reported in this case, the use of a dosing cup that is not packaged with the product has resulted in overdose. Therefore, DMETS believes the lack of a product-specific measuring device increases the potential risk for dosing errors.

The design of dosing devices used to administer cough and cold products to children are also a source of error for parents and caregivers. For instance, the dosing directions for "infant drops" formulations have changed over the years. Historically, these products were dosed by the number of drops. Currently, the Drug Facts label of these products dose the product in milliliters (mLs) and may include reference to the packaged dosing device. In some older cases (ISR #'s 4921552-9 and 1836779), parents reportedly administered squirts from the dropper provided rather than the actual number of drops ordered resulting in an overdose to these children. DMETS notes the products described as "drops" today are dosed in terms of dropperful, milliliter (mL), or teaspoonfuls for these products. These units of measurement are inconsistent with the dropper device provided in the package, which can measure only in 0.8 mL increments and is a source of confusion. The Internet message boards also describe the challenges parents have manipulating the dropper devices when attempting to withdraw the correct amount of the drug product. Based on these findings, DMETS questions whether the dropper is the best measuring device for delivering doses to this young patient population.

Lastly, the nomenclature of the cough and cold product can also lead to dosing errors. For example, the formulation "drops" has more than one corresponding routes of administration (i.e., oral, optic, otic and intranasal). In one case (ISR # 4863259-2), the caregiver's familiarity with decongestant "drops" being used intranasally led him to mistakenly assume that oral drops were a topically administered product. Thus, the product was administered intranasally and lead to the infant having difficulty breathing until the product was manually aspirated. DMETS believes labeling these concentrated oral liquids for younger children as something other than "drops" may reduce the potential for these products being administered via an incorrect route of administration. However, such a change in nomenclature of this oral formulation would require broader input and evaluation from other offices within CDER and the public prior to implementation.

4.2.1 Formulation/Product line issues

Parents' comments on the Internet stated the number of cough and cold products available can be overwhelming. Thus, parents often become familiar with and often rely on specific product lines. However, they may not be aware that their familiar brand contains ingredients that differ from what they expect it to contain. The proprietary name of monograph products can be used to describe more than one product that contains different active ingredients (e.g., Pediacare, Dimetapp, and Triaminic) or the composition of the product may change without a name change. A number of OTC cough and cold product lines have well-recognized proprietary names in the United States, a number of which are also monograph products. As monograph products, the Agency does not review the labels and labeling prior to commercial marketing. As a result, products within a product line may be confused when there are formulation changes, products have similar names or symptom descriptions, or products have more than one concentration for a specific medication (Infant's vs. Children's)

In some cases, sponsors have changed the ingredients or amounts of ingredients in products without notifying health care providers and/or consumers and with or without changing the product name or label design. Some formulation changes are a result of regulatory actions such as the removal of phenylpropanolamine from the market or limiting the distribution of pseudoephedrine containing products. Although sponsors may highlight the changes made to the formulation with a "New Formula" statement on the primary display panel of the label, a parent's reliance on a specific formulation within a product line can lead them to overlook the well labeled changes in the ingredients and/or the prominence of this warning may be insufficient. An example of this type of error occurred following the reformulation of a chewable tablet a 5 year old had been taking as directed by a physician. The family switched to a new box completely unaware that this new box contained the reformulated tablets (ISR # 4633819-2). The reporter stated it "had too much medication in each tablet." Therefore, DMETS believes formulation changes that are not well publicized, lack prominent warnings on the label, and products that continue to use the same proprietary name despite the change in active ingredient or potency, increase the potential for dosing errors.

Some parents may select cough and cold products based solely on their familiarity with a specific brand name or product descriptor (i.e., Nighttime, Children's). In some cases, parents utilize different combination products within a product line assuming that all the products are appropriate for use in all age groups. In addition, the doses and frequency of administration may also be interchanged by the parents. Parents switch combinations within a product line based on the name of the product or symptoms listed on the container and may not realize that within the same product line there may be different age-based dosing instructions. For instance, cough and could products containing antihistamines such as diphenhydramine are not labeled for use in children under the age of six. However, products containing the descriptors "Nighttime" or "Night" in the name often contain diphenhydramine or another antihistamine. However, parents use these products because they have used products containing "Nighttime" as part of the name in the past to treat their child's symptoms at night (ISR# 4230551-4). In addition, a comment pulled from the Internet states the parents selected a specific product because it had "Nighttime" in the name. The selection of these "Nighttime" products may occur when parents have been instructed by a prescriber in the use of another combination product, one not containing an antihistamine, from that family name. The parents use the same dose and frequency for both products because they are unaware of the differences, without confirming the dose with the labeling or prescriber.

Parents/caregivers also confuse the concentrations of infant's and children's formulas of cough and cold products within a specific product line or brand. For example, a prescriber dosed a 19 month-old child using the concentration of the Children's formulation of a cold product familiar to them as ¾ of a teaspoon. However, the family purchased the Infant's formulation of

the same product line (ISR # 4955917-6) which is much more concentrated that the Children's product Although the prescriber provided detailed instructions for use, the family obtained the incorrect concentration of the needed medication and overdosed their child. DMETS notes several product lines that contain both Children's and Infant's concentrations have modified the names to begin with "Infant" or "Toddler" in an attempt to better differentiate these concentrations. However, DMETS believes discontinuing the more concentrated "Infant's" formulation will eliminate this confusion and reduce the risk of overdoses attributed to the inadvertent use of the more concentrated product.

Finally, parent comfort with and reliance on specific over-the-counter products may lead them to falsely believe that these products are free of risk. Therefore, parents and caregivers use products intended for older children in the family to treat symptomatic infants. In these cases (ISR #'s 5269019-5 and 4417552-8), the caregivers administered the medications without consulting the child's pediatrician. Caregivers incorrectly believe if an over-the-counter product is safe to give to an older child or sibling then it should be safe to administer to an infant. Unfortunately, the use of "Children's" products intended for an older sibling has resulted in the death of the child when the parent or caregiver dosed the medication without obtaining a physician's recommendation.

4.2.2 Wrong Drug

The nomenclature of OTC cough and cold products is not reviewed by the Agency prior to commercial marketing. Many cough and cold products include the symptoms they relieve in the proprietary name, and parents may select the product on this basis without reading all the detail provided in the Drug Facts labeling. As a result, the nomenclature of the product may inadvertently lead to product selection errors. In some cases, parents select a cough and cold product to treat a fever, simply because they associate fevers as a symptom of cough and cold illnesses. In one case (ISR# 4755459-7) the use of a cough and cold product, Pediacare Nightrest Cough-Cold, was ineffective in reducing a child's fever as it did not contain any fever reducer ingredient in the product. Conversely, errors have also occurred when parents have used a multiple ingredient products to treat an isolated symptom (e.g. fever) thereby exposing the child unnecessarily to multiple active ingredients. In one case, a parent selected a product containing "cold and fever" in the name to treat a viral fever (ISR# 3874984-4). As the fever did not reduce after the first dose, the parents gave the product more frequently than labeled to speed reduction the fever. The parents' concern for reducing the fever contributed to the parent overlooking that the product contained other active ingredients (a decongestant and cough suppressant) that caused adverse effects when administered in excess.

Similarly, the packaging of monograph OTC cough and cold products is not reviewed by the Agency prior to commercial marketing, and thus some aspects of the labeling have contributed to error. Aspects such as the label statements referencing well known proprietary names has contributed to errors as well. The statement, "From the makers of Neo-Synephrine," confused a pharmacist and nurse in a hospital when phenylephrine drops were ordered by a physician (ISR# 3942371-6). Although the product dispensed, a saline solution, was well labeled with the proprietary name, NaSal, both healthcare providers focused on the name "Neo-Synephrine," thus, overlooking the fact that this product did not contain the intended phenylephrine ordered by the physician. The prominence of "From the makers of" statement contributed to this error. Although this error occurred in a hospital setting, the possibility exists for the same type of error to occur in an outpatient pharmacy or grocery store. Thus, OTC products should avoid inclusion of such comparative statements when the comparative product does not contain the same active ingredient as the product being labeled.

4.3 ASK YOUR PHYSICIAN LABELING

In accordance with the Drug Facts labeling implementation, the statement "Ask/Consult your physician" appears on the labeling for all cough and cold products that are not labeled with dosing instructions for children less than 2 years or 6 years if the product contains diphenhydramine. However, it is clear that this warning has not be successful in preventing medication errors since twenty of the cases identified in AERS describe the use of the product in these age groups without consultation from a physician.

DMETS believes it is possible that some parents may not read the "Ask your physician" statement as evidenced by many of the contributing factors identified from the AERS cases. Parents dose a child based on the symptoms they wish to relieve with the list of symptoms relieved on the primary display panel of the packaging, parents do not read all the detail provided in the Drug Facts labeling. When they read the statement, parents have commented that contacting a physician prior to using a product may be inconvenient. Other parents felt uncomfortable contacting if physician has seen the child or was recently seen by their physician multiple times for cold symptoms. Appendix 3 contains full citations. Both situations may cause parents to ignore the "ask your physician" directions on the label. Therefore, some parents look for alternate products that may include doses for their children's age groups.

DMETS also identified cases in which an OTC product is prescribed by a physician , but the caregiver purchases and/or uses a different combination product within the same brand name product line without reconsulting the physician (ISR # 4883158-X). Stronger wording of the "Ask you physician" statement may better encourage parents to heed this advice and decrease the potential to overdose in children under the age of six

However, even when the physician is contacted, there is still potential for error with cough and cold products for several reasons. The prescriber may not be familiar with all product combinations, prescribers may recommend only one concentration of a certain product, or not be aware of any product reformulations. Additionally, when the prescriber provides directions either written out for the parent or written on a prescription, both the parent and the pharmacist may misinterpret the directions for use because the doing units are misinterpreted or abbreviations unknown to parents are used to communicate the dosing interval of the product. DMETS identified a case in which the prescribers handwriting resulted in misinterpretation of the units of measure (mg for mL) resulting in an overdose (ISR# 3668839-8). In addition, when the physician provided parents with written directions for use including the abbreviation "HS," the parents did not understand that "HS" meant at bedtime and simply relied on the frequency listed in the Drug Facts labeling resulting in administration of the product too frequently (ISR# 5004565-0). Also when the parent contacts a healthcare provider to determine a dose on a particular OTC product, the dose provided may not be correct for the concentration of the product the parent has on hand [Children's Dimetapp vs. Children's Dimetapp Infant (ISR # 4955917-6)]. Thus, even when a healthcare prescriber is contacted, the prescriber's advice may contribute to errors.

Rather than provide patient- and product-specific dosing information on a case-by-case basis, some healthcare providers predetermine doses or provide dosing charts. In some cases, the predetermined doses are incorrect, or are improperly transferred across product lines. A case involved the parents administering a dose incorrectly determined by a pharmacist at the pharmacy (ISR# 5079642-9). Additionally, physicians' offices provide dosing charts to parents to assist them in determining the proper dose for their child (Appendix 3). Once parents have these dosing charts, the parents may be less inclined to seek a physician's input to determine if the child needs the selected product or if the dose is appropriate. Through our review of the medication errors cases from AERS and the comments from the Internet, DMETS believes that parents dose

medications using the same dose across different products within a product line as well as across to different product lines without reading the Drug Facts labeling which results in dosing errors. In an effort to relieve the child's symptoms, parent utilize sources other than the Drug Facts labeling to obtain a dose of OTC cough and cold product for their child.

5 CONCLUSION

Medication errors involving over-the-counter use in children younger than 6 years of age occur for many different reasons, and negatively impact the safe use of cough and could products in the pediatric patient population. The cases reviewed identified multiple contributing factors to these errors such as concurrent use of therapies containing the same active ingredients or therapies within the same therapeutic class, dosing errors related to misinterpretation of direction for use and measuring devices, formulation changes, and product line confusion. Clearly, the number of OTC cough and cold products made available to the consumer is another contributing factor to these errors. DMETS notes overdoses related to concurrent therapy most frequently occur with the use of multiple ingredient products. While the regulations for the monographs of cough and cold products specify the listing of ingredients and what is included in the Drug Facts labeling, some sponsors more clearly list the active ingredient with the symptoms it treats on the primary display panel. In addition, the current labeling statement of "ask/consult your physician" does not effectively foster the communication between the caregiver and healthcare providers specifically physicians nor does it guarantee that even if a physician is reached it will minimize dosing errors in products that do not provide specific dosing instructions in all age groups. There is also evidence that many parents and caregivers do not read or may not understand all of the information in the Drug Facts labeling prior to administering the product to children.

These findings support the Petitioner's opinion that unintentional overdoses occur in this patient population. DMETS identified contributing factors to these overdose errors which were in addition to the use of "infant" and "baby" in the product name or the image of a child less than six years of age on the label discussed by the petitioner.

6 RECOMMENDATIONS

DMETS has the following recommendations in an effort to reduce user error and improve patient safety with the use of Over-the-Counter cough and cold products:

- As dosing devices continue to contribute to medication errors, DMETS recommends all OTC products for children should contain a dosing device consistent with the product labeling. For example, droppers for drops or concentrates, oral syringes or dosing cups for other oral liquids. In addition, Healthcare provider should be educated in the dosing devices provided with these products.
- In an effort to reduce the confusion between "Children's" and "Infant's" concentrations of a medication, consideration should be given to standardizing the concentrations of ingredients in OTC cough and cold products. The preferred approach from a medication errors perspective would be to remove of the concentrated "Infant's" formulation to reduce the potential of overdose from inappropriate selection of the concentrated formulation.
- Active ingredients should appear with equal prominence along with the symptoms they relief on the primary display panel on all cough and cold products for use in children. This may help increase caregiver awareness of the active ingredients contained in cough and cold product, and enable them to make more appropriate decisions when selecting the OTC products. An overdose warning should also be added to the labels and labeling that instructs patients to compare the active ingredients of all products and not to use the

product if it contains an active ingredient contained in another product they are currently using.

- Due to the heightened risk of overdose due to concurrent therapy with multi-ingredient cough and cold products, DMETS recommends the Agency consider elimination of multi-symptom products for use in children under 6 years of age.
- Encourage sponsors to study cough and cold products in children under six to provide adequate dosing instructions if these products prove to be safe and effective in this age group. In the interim, communication between caregivers and healthcare providers will be key in reducing errors involving OTC cough and cold products in children under the age of six years, and the current "ask your physician" statement can be improved to stress the importance of this communication. The ask your physician statement could be modified to read, "Consult your physician prior to using this product." In addition, DMETS recommends adding a statement in the Warning section of the Drug Facts labeling that reads "The wrong dose of this medication in children may cause harm, contact your physician prior to use."

7 REFERENCES

1. Adverse Events Reporting System (AERS)

   AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. OSE Safety Review #2007-1022, Postmarketing Safety Review of Serious Adverse Events in Children Less than 6 years of age Associated with the use of Cough and Cold Medications, Akhavan-Toyserkani, G, Chang,YJ, DDRE

3. OSE Safety Review #2007-1022, Over-the-counter and prescription use of cough/cold products, Governale,L. DCRCS

4. www.epinions.com, August 6, 2007

APPENDICES

APPENDIX 1

Drug Facts Containing Labeled Doses by Age for Some Common OTC Pediatric Cough and Cold Products

Product	Active Ingredients	< 2 years	2 to 5 years	6 to 12 years
Children's Benadryl®	Diphenhydramine	no	no	yes
Children's Dimetapp® Cold and Allergy	Brompheniramine/ Phenylephrine	no	no	yes
Toddler's Dimetapp® Decongestant Drops	Phenylephrine	no	yes	Not labeled
Children's Tylenol® plus Cold (with phenylephrine)	Acetaminophen/ Phenylephrine	no	no	yes
Children's Tylenol® plus Cold (with pseudoephedrine)	Acetaminophen/ Pseudoephedrine	no	yes	yes
Concentrated Tylenol® Infant Drops plus Cold	Acetaminophen/ Phenylephrine (or Pseudoephedrine)	no	yes	Not labeled
Delsym®	Dextromethorphan	no	yes	yes
Neo-Synephrine® Mild Formula Nasal Spray	Phenylephrine	no	no	yes
Pediacare® Infant Decongestant plus Cough (PSE)	Pseudoephedrine/ Dextromethorphan	no	yes	Not labeled
Pediacare® Multi-Symptom Cold	Phenylephrine/ Dextromethorphan	no	yes	yes
Robitussin® Pediatric Cough and Cold CF	Phenylephrine/ Dextromethorphan/ Guaifenesin	no	yes	Not labeled
Robitussin® Pediatric Cough and Cold Nighttime	Phenylephrine/ Dextromethorphan/ Chlorpheniramine	Do Not Use	no	yes
Triaminic® Daytime Cold and Cough	Phenylephrine/ Dextromethorphan	no	yes	yes
Triaminic® Nighttime Cold and Cough	Phenylephrine/ Diphenhydramine	no	no	yes

APPENDIX 2 Details of AERS Cases Identified including Narrative Summary

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
11/30/2005 4841819-2	15 months	Tylenol (acetaminophen), Triaminicol (phenylpropanolamine, pheniramine, pyrilamine, and dextromethorphan), and Contac Jr. (phenylpropanolamine and acetaminophen)	Improper Dose-Overdose	concurrent therapy	The child was given multiple cold medications including several containing acetaminophen for four weeks for intermittent cough and fever associated with pneumonia. Patient also received a ten day therapy of ampicillin. The child developed acute liver failure and encephalopathy from chronic acetaminophen ingestion. The child was treated for ten days in the hospital and released. (A literature case)
5/31/1999 3975892-0	4 years	Triaminic Cold and cough –Purple. (diphenhydramine and pseudoephedrine Robitussin Cough and Cold (guaifenesin, dextromethorphan, and pseudoephedrine)	Improper Dose-Overdose	concurrent therapy	The child was diagnosed with a sinus headache and otitis media. The child was prescribed Ceftin for ten days and Triaminic Cough and Cold. The child was also receiving Robitussin Cough and Cold. The child complained of a headache and became unconscious on route to the emergency room. The child was had a subarachnoid bleed and died three days later.
10/5/2003 4860806-1 Same case in OSE review 2007-1022 ISR# 4861466	3 months	Tylenol Infant's Plus Cold (pseudoephedrine/ acetaminophen) and Pedia Relief (pseudoephedrine/ dextromethorphan)	Improper Dose-Overdose	concurrent therapy	The child had been sick for 2-3 days. The child received 15 mL of Pedia Relief and 7.5 mL of Tylenol Infant's Plus Cold 2 days. The child found unresponsive face down in a pillow. The cause of death was acetaminophen Poisoning, The post-mortem pseudoephedrine blood levels were at adult therapeutic levels.

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
4/11/2005 4645107-9	12 weeks	Pseudoephedrine and Diphenhydramine.	Wrong Time/ Frequency	concurrent therapy	The child received one half dropperful Pediacare decongestant and Benadryl at the same time. Another dose of Pediacare was administered two hours later. The child would not wake up. Pediacare discontinued and no outcome was reported.
5/13/2005 4678862-2	1 year	Diphenhydramine and (Rx) chlorpheniramine tannate, mepyramine tannate and phenylephrine tannate	Monitoring Error (duplicate therapy)	concurrent therapy	The child had been receiving one half teaspoon of Benadryl as needed for running nose. The child was ordered Rx Rynatan for congestion. The child became agitated and hyper. Physician advised to stop Benadryl and continue Rynatan. The events resolved in 24 hours.
1/18/2006 4883158-X	6 months	Infant's Tylenol Cold (pseudoephedrine/ acetaminophen) and Carbaxefed RF (Carbinoxamine/ Pseudoephedrine)	Improper Dose-Overdose	concurrent therapy	The child was diagnosed with pneumonia and prescribed Tylenol, Motrin, Pedialyte, amoxicillin, and Carbaxefed RF. The child received Infant's Tylenol Cold "according to the instructions on the box." The child was inconsolable then became listless. The brought to the emergency room. The child died from a pseudoephedrine overdose.
12/1/2006 5192119-5	21 months	Diphenhydramine	Improper Dose-Overdose	concurrent therapy	The child had been receiving Benadryl since 9 months of age. Child developed a cold and was started on a cough medication which may have contained diphenhydramine. The patient developed a rash and hives and was treated with Benadryl allergy. No adverse event was reported, but child went to the emergency room for treatment of the unresolving hives.

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
1/12/2007 5296267-0	6 months	OTC acetaminophen/ pseudoephedrine and prescription pseudoephedrine/ carbinoxamine/ dextromethorphan	Improper Dose-Overdose	concurrent therapy	A six month old girl overdosed on pseudoephedrine and dextromethorphan after received both an over-the-counter cold medication in addition to a prescription cough and cold medication. The child died. The cause of death was pseudoephedrine and dextromethorphan intoxication.
11/30/1984 313575	6 weeks	Triaminic infant drops (pheniramine and pyrilamine)	Improper Dose-Overdose	dosing error	Triaminic oral infant drops were labeled by a pharmacist to give 4 drops four times a day. Mother giving infant four squirts on three separate times. The child died from an acute overdose of pheniramine.
11/1/1985 387222	6.5 months	Actifed (triprolidine/ pseudoephedrine)	Improper Dose-Overdose	dosing error	Patient taking two medications for Otitis media. Caregiver confused the dose of Septra suspension (6 mL) for the dose of Actifed (1.25 mL). the child developed torticolis and was taken to the emergency room.
1/8/1995 1836779	5 months	Triaminic Oral Infant drops (phenylpropanolamine, pheniramine, and pyrilamine)	Improper Dose-Overdose	dosing error	Child died after caregiver gave squirts or dropperfuls for a dose intended to be three drops. Blood levels of phenylpropanolamine high.
2/15/2001 3668839-8	3.5 years	pseudoephedrine	Improper Dose-Overdose	dosing error	A prescription written for the medication (30 mg/5 mL) was misread. The dose intended as 15 mg was mistaken for 15 mL. The child received one dose and became irritable. The mother contacted the pharmacy and the directions were corrected.
2/16/2002 3885078-6	62 weeks	pseudoephedrine	Improper Dose- Under Dose	dosing error	Mother gave 0.4 mL of Pediacare Infant Decongestant plus Cough although the physician prescribed 0.8 mL for congestion. The child also received Tylenol. The child developed tachycardia and was taken to the emergency room.

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
2/6/2006 4921552-9	6 months	Pseudoephedrine/ dextromethorphan	Improper Dose- Extra Dose	dosing error	Child spit out part of dose and grandmother attempted to supplement
7/31/2006 5079642-9	5 months	Infant's Pediacare Decongestant and Cough Drops (Pseudoephedrine and Dextromethorphan)	Improper Dose- Overdose	dosing error	The child received a dose recommended by pharmacist (2-3 dropperfuls). The child had a dazed look and was taken to the pediatrician's office for evaluation.
5/9/2006 5004565-0	20 months	Dimetapp (brompheniramine/ decongestant)	wrong time/ frequency	following frequency on label not as instructed.	The child saw the pediatrician. The physician gave the father a note stating "Dimetapp ¾ tsp HS." Parents not familiar with meaning used frequency on the label "every four hours." the child received a dose before bed that evening, a dose in the morning and was sent to daycare with instructions to give every four hours. Reporter found out what HS meant and call pediatrician's office to clarify the Dimetapp should only be given at bedtime. No outcome reported.
3/22/2005 4633819-2	5 years	Triaminic Cough and Sore Throat pseudoephedrine/ dextromethorphan/ acetaminophen	Improper Dose- Overdose	formulation change	The child was given 1 tablet every five hours. He received one dose from an old box. And started a new box. the child had a seizure. the mother stated that the new box "had too much medication in each tablet." The child was taken to the emergency room and discharged the next day.
6/6/2006 5032051-0	30 months	Triaminic Cold and Cough cherry pseudoephedrine/ dextromethorphan/ chlorpheniramine	Improper Dose- Overdose	formulation change	The child received 5 ml every four to six hours as directed by physician. She began breathing "heavy and irregular." She had taken the medication previously without a problem. No outcome reported.
3/28/1997 4168717-4	5 years	brompheniramine/ phenylpropanolamine	Improper Dose- Overdose	measuring device.	caregiver used measuring device from another product which resulted in patient receiving 3 teaspoons vs. 1 teaspoon

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
2/14/1998 3003218-8	3 years	dextromethorphan	Improper Dose-Overdose	measuring device.	The child was being treated for bronchitis. He received a dose of 2 capfuls measured by using the bottle's cap. The child began acting "dopey" and his pupils were dilated. The child was taken the emergency room and given naloxone. The child was monitored overnight and discharged the following day.
5/14/2004 4363124-3	1 year	Dimetapp Infant Drops (pseudoephedrine)	Improper Dose-Overdose	measuring device.	This product is labeled as drops. The physician directed to take 1 and one half dropperfuls (1.2 mL). This product comes with a 1.6 mL syringe that measures mLs. The child received one and a half syringes (2.4 mL).The reporter stated the dosing device was confusing.
9/21/2006 5122319-1	18 months	Pseudoephedrine/ dextromethorphan	Improper Dose-Overdose	Measuring issues	Father stated he accidentally treated his daughter with 2 tablespoons of Pediacare (Rather than 2 teaspoons)
3/16/2002 4163489-1	3.5 years	Tylenol Cold (acetaminophen and pseudoephedrine) and Dimetapp (brompheniramine and pseudoephedrine)	Improper Dose- Extra Dose	Multiple caregivers	The child was found lethargic limp uncoordinated and slurred speech. by mother. The child had received Dimetapp from the fathers girl friend and Tylenol Cold from his father within a few hours of each other for a cough. No outcome was reported.
1/16/2006 4898544-1	2 years	diphenhydramine	Improper Dose- Extra Dose	multiple caregivers	The child was given Benadryl three times daily for an allergic reaction to Augmentin. The mother and housekeeper both gave child doses within an hour of each other. No adverse outcome reported due to this extra dose.
7/6/1998 4110788-5	2 years	diphenhydramine	Wrong Time/ Frequency	None identified	The nurse gave a dose of diphenhydramine 12.5 mg prescribed every 6 hours three hours after previous dose. No outcome reported.

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
6/23/2002 3942371-6	1 month	sodium chloride nasal/ phenylephrine nasal	Wrong drug	Product Line confusion	Physician ordered ¼% Neo-Synephrine drops. the pharmacy dispensed and the nurse administered NaSal saline moisturizer for three days.. The box stated "from the makers of Neo-Synephrine". Reporter stated "from the makers of" was in small print compared to the "Neo-Synephrine"
10/10/2003 4230551-4	2 years	Triaminic Cold and cough (pseudoephedrine and dextromethorphan) and Triaminic Cold and Night Time Cough (pseudoephedrine and diphenhydramine)	Improper Dose-Overdose	Product Line confusion	The mother treated the child with Triaminic Cold and Cough 1 teaspoon in the day, and Triaminic Cold and Nighttime Cough 1 teaspoon at bedtime. The Nighttime formulation not labeled for child this age. The child developed trouble breathing in doctor's office and was taken to the emergency room. Patient had a febrile seizure Patient was treated with Tylenol and he had no further seizure activity.
1/28/2006 4908951-6	11 months	Pseudoephedrine/ dextromethorphan	Improper Dose-Overdose	product line confusion	The father stated he had been giving 8 ml (?0.8 mL) three times daily of Infant's Pediacare Long-Acting cough to his daughter. He gave her 8 ml Pediacare Long-Acting Cough plus Cold by mistake thinking it was formula. Child would not sleep.
8/12/2005 4755459-7	3 years	pseudoephedrine/ dextromethorphan/ chlorpheniramine	wrong drug	Product Line confusion	The child was treated for a fever with Pediacare Nightrest Cough-cold. The fever went up to 106 and the child was taken to the emergency room where he was treated with ibuprofen. Selected product does not contain acetaminophen or ibuprofen.
3/22/2006 4955917-6	19 months	brompheniramine/ pseudoephedrine	wrong strength/concentration	Product Line confusion	A physician prescribed a dose of 3/4 teaspoon Children's Dimetapp for this child. the family purchased DIMETAPP Infant formula. The reporter stated "Children's Dimetapp" should not be in the name of the infant's formula.

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
8/21/2001 3874984-4	4 years	Triaminic Severe Cold and Fever (Pseudoephedrine, Dextromethorphan, Chlorpheniramine, and acetaminophen)	wrong drug	symptom in name/product line confusion	Mother giving her son with multi-ingredient product every 2.5 to 3 hours for the treatment of his fever due to a viral infection. Child began shaking with eye rolling back. seizure treated with Diazepam. Seizure activity did not stop. He was transferred to another hospital.
3/19/2007 5269019-5	3 months	Pseudoephedrine and dextromethorphan	Improper Dose-Overdose	used an older siblings medication	A baby had a cough and was prescribed an antibiotic, Vantin. Parents treated cough with a medication taken by an older sibling. Child died of pneumonia but had high levels of pseudoephedrine in the blood.
8/3/2004 4417552-8	20 months	Dextromethorphan	Improper Dose-Overdose	used mediation for older child (foreign)	The child had an upper respiratory infection. Babysitter gave 1 mL (3mg/mL) dextromethorphan of daughter's medication to the toddler 13 hours apart. The child was found 6 hours after last dose dead in the bed. The child dies of dextromethorphan overdose. A literature case. (Canadian)
10/14/2002 4104164-9	26 months	diphenhydramine	Wrong Route of Administration	Product container	Benadryl topical gel was given orally accidentally at a daycare center. The child was taken to the emergency room, treated and released.
12/7/2005 4863259-2	49 days	pseudoephedrine	wrong route of administration	Formulation name	Grandfather administered drops intranasally rather than orally. Product was suctioned from the nose when she was having a hard time breathing. She was taken to the doctor's office, then the emergency room.

Date ISR #	Patient age	Medication involved	Error type	Contributing Factors	Summary of narrative
1/1/2003 4575714-3 Same case in OSE review 2007-1022 ISR# 4477566	2 years	pseudoephedrine/ diphenhydramine/ phenylpropanolamine	improper Dose-Overdose	Product content transferred to a container without a child resistant closure.	A two year old found in her vomitus. The child had high post mortem concentrations in the blood of pseudoephedrine and dextromethorphan. The family had multiple cold products in the home which had been transferred from the original container to non-child resistant bottles.

APPENDIX 3: Parent and Caregiver comments found on www.epinions.com on August 6, 2007

Determining the Dose from the Labeling
My 5 month old son has had continuous congestion and cough. After exhausting every effort I could think of (humidifier, numerous trips to the pediatrician, other medicines, tilting the crib mattress, etc...), I just happened to come across Children's Sudafed at Wal-Mart. At first I hesitated to buy it since it is meant for children over 2. However, since I was desperate for relief for my son AND myself, I took matters into my own hands. I decided to give my son the dose I would normally give him with PediaCare it worked!
Unlike many medications that are geared toward kids but only offer dosing instructions for "6 years and up" (what kind of confidence does THAT give me?) Triaminic has dosing instructions for ages 2 years and up, based upon weight.
Once I had opened the box and was getting ready to give my daughter her first dose I realized that they didn't have a recommended dosage for an infant her age! Why bother calling it Infants' if it doesn't even have dosage instructions for an infant? I called my pediatrician who recommended only one dropperful for her age and weight.
Since my daughter is less than two years old, I was certainly glad I had asked the nurse at our pediatrician's office about the correct dosage amount prior to purchasing this product. In our case, one dropperful (0.8 mL) was recommended.
Infants under 2 have to consult a physician for dosage (how convenient).
The dosage directions start with 6 year olds, but your doctor can give you a chart that breaks it down into younger kids and their dosages (it's mostly a weight thing).
...for younger kids, your pediatrician (or pharmacist) should have a chart (based on weight) to tell you how to dose correctly.
The Variety of Products Available and the Impact on Choosing the Product
I hate spending money on separate cold medicines for each member of the household. One for infants, one for toddlers, one for children, and one for adults.
At the grocery store, pharmacy or discounts store, you are overwhelmed with choices to treat your child's symptoms. Being a protective parent, you do not want to overmedicate your child, but know that you want the medicine that will work the best and last the longest. You see yellow, orange, red, pink and purple liquids; cherry, grape, fruit and bubble gum flavors; brands that work four hour and some that work six; chewables, liquids that your child will take a 1/2 teaspoon and liquids that your child will need a whole teaspoon; and last you will find decongestants, expectorants, cough suppressants, cough expectorants and fever reducers.
He was up all the time, his poor nose was looking like rudolph, he couldn't rest and just plain driving me up the wall since he was so whiny. We bought the Nighttime Pedia Care also for bedtime thinking this would help him at nighttime.
My oldest daughter has a hard time of going to sleep at night and has been taking Benadryl to help her sleep since she was two.
Children's NyQuil is recommended for children ages 6 and up, but my daughter fits in the weight category for 6 - 12 year olds.
Unwilling to call the pediatrician and admit that he had been right, I sent my husband to the drug store to find something appropriate for a young baby's cold. When the goop that returned with hadn't worked in about three days though, I swallowed my pride and called the doctor's office.

Measuring Devices and Product Packaging
As you already know if you've ever administered liquid using a dropper, filling it to the correct amount is rather difficult, and this product was no exception. Even though I was directed to administer a full dropper of the medication, that pesky air bubble ensured that I squeezed and squeezed for several minutes before I was finally happy with the amount in the dropper.
In my experience, this formula has been approved and is effective for younger children as long as you follow the guidance and direction or your pediatrician. The product comes with a dispensing cup that rests on the childproof cap of the medicine. (QUICK NOTE: If I don't fasten the cap tight, my son can open this medicine which is quite disconcerting to me. I have made a special effort to secure the lid now and place the medicine out of his reach.) You will see that this dispensing cup illustrates several measurements that may be appropriate based on the given dosage specified by your physician.
How prescribers give dosing directions
Before bedtime, I read the box and put 1 drop in each of my daughter's nostrils. The directions advised to consult a physician for infants and didn't specify how much to give to a 6-month-old, but at our last checkup, our pediatrician had mentioned Little Noses and said to simply give the smallest dosage when giving my daughter any infant decongestant. (CONSULT YOUR OWN PHYSICIAN BEFORE USING ANY MEDICATION).

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 9, 2007
To:	Joel Schiffenbauer, M.D., Deputy Director Office of Non-Prescription Drug Products Office of New Drugs
Thru:	Solomon Iyasu, MD, MPH, Director Division of Surveillance, Research and Communication Support Office of Surveillance and Epidemiology
From:	Laura A. Governale, Pharm.D., MBA, Drug Use Data Specialist Team Leader Division of Surveillance, Research and Communication Support Office of Surveillance and Epidemiology
Subject:	Over-the-counter and prescription use of cough/cold products
Drug Name(s):	Brompheniramine, Chlorpheniramine, Dextromethorphan, Diphenhydramine, Pseudoephedrine, Phenylephrine, Clemastine, and Guaifenesin
Submission Number:	Multiple
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
OSE RCM #:	2007-1022

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CONTENTS

EXECUTIVE SUMMARY

The sale of OTC and prescription products containing cough/cold ingredients have fluctuated over the last 5 years, 2002 through 2006. The majority of cough/cold ingredients were sold as OTC products and only 19% were sold as prescription products.

Of the OTC cough/cold market, the majority of cough/cold products are in multiple-ingredient/combination product formulations. The proportion of sale of single-ingredient OTC cough/cold products remained relatively consistent for the years 2002 through 2006, except for pseudoephedrine and phenylephrine. Of the single-ingredient OTC product market, the most widely sold active ingredient over the last 5 years was diphenhydramine. For the multiple-ingredient/combination OTC cough/cold market, dextromethorphan was the most common active ingredient for the entire 5 years analyzed.

Assuming that only children under the age of 2 years are consuming oral drop formulations, less than 1% of all liquid dosage forms sold for dextromethorphan, pseudoephedrine, phenylephrine, and guaifenesin were formulated as oral drop formulations during year 2006 for both single-ingredient and combination cough/cold products.

The most commonly dispensed prescription cough/cold products in year 2006 were combination guaifenesin products, accounting for 29% (9.5 million dispensed prescriptions) of the cough/cold market. Cough/cold prescriptions dispensed to the 0-6 year age group accounted for approximately 3.9 million dispensed prescriptions or 12% of the entire cough/cold market in year 2006. The most commonly dispensed cough/cold product in the pediatric age 0-6 years population was the phenylephrine combination products. Concurrent use of OTC medications cannot be captured using the available databases. Therefore, a truly reliable estimate of concurrent medication use with cough/cold products is not possible.

1 BACKGROUND

In response to a request for drug use data by the Office of Non-Prescription Products (DNP), this consult examines the over-the-counter (OTC) and prescription utilization of pseudoephedrine, ephedrine and phenylephrine containing products from years 2002 through 2006. Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

1.1 INTRODUCTION

The Office of Non-Prescription Products (ONP) is examining reports of serious adverse events in children under the age of 6 years old using over-the-counter (OTC) and prescription cough/cold medications. In support of this examination, drug use data were also requested by ONP to evaluate the sale and prescription usage of cough/cold products containing the following active ingredients from years 2002 through 2006: pseudoephedrine, dextromethorphan, chlorpheniramine, and diphenhydramine. For the sake of completeness, also included in this analysis were brompheniramine, phenylephrine, clemastine, and guaifenesin. Utilization information on cough/cold products containing these active ingredients will be presented and used as background material in preparation for the Non-Prescription Drugs Advisory Committee meeting, to be held on October 18 -19, 2007.

In support of this meeting, this review provides an overview of the sale of OTC combination and single-ingredient cough/cold products containing pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, brompheniramine, phenylephrine, clemastine, and guaifenesin as well as the trends in outpatient usage for prescription combination products for years 2002 through 2006. For the purposes of this review, cough/cold products will be referred to

as those products containing the aforementioned active ingredient molecules. Proprietary drug use databases licensed by the FDA were used to conduct this analysis.

2 METHODS AND MATERIALS

2.1 DATA SOURCES USED

Outpatient data sources were used to examine the use of OTC cough/cold products using the IMS Health, IMS National Sales Perspectives™ data (see Appendix 1). Extended units (tablets/capsules/milliliters of solution) of cough/cold products sold from the manufacturers into the various retail and non-retail channels of distribution were analyzed from years 2002 through 2006. Products were categorized as single-ingredient versus combination and analyzed by active ingredient molecule, and dosage forms.

For prescription products containing these cough/cold ingredients, outpatient use and patient demographics were measured using the Verispan, LLC: Vector One®: National (VONA) and indications for use were obtained from the Physician Drug and Diagnosis Audit (PDDA) (see Appendix 1). Through these sources, estimates of the number of dispensed prescriptions by retail pharmacies and the number of drug mentions by office-based physicians were analyzed from years 2002 through 2006. Prescription cough/cold products were all categorized as combination and analyzed by class, prescribing specialty, patient age[1] and indications for use; there are no prescription-strength single-ingredient cough/cold products, however, any OTC product may be dispensed as a prescription under a physician's order.

2.2 PRODUCTS INCLUDED

For the purposes of this review, cough/cold products will be referred to as those products containing the following active ingredient molecules: pseudoephedrine, dextromethorphan, chlorpheniramine, diphenhydramine, brompheniramine, phenylephrine, clemastine, and guaifenesin.

3 RESULTS

3.1 SALE OF OTC AND PRESCRIPTION COUGH/COLD PRODUCT INGREDIENTS

The sale of OTC and prescription products containing cough/cold ingredients have fluctuated over the last 5 years, 2002 through 2006 (Appendix 2: Table 1). Sales in terms of individual tablets, capsules and milliliters of solutions sold reached a high of 36 billion extended units in year 2003 and fell to a low of 30.5 billion extended units in the following year. The majority of cough/cold ingredients were sold as OTC products. During year 2006, nearly 33 billion extended units of products containing cough/cold ingredients were sold, of which, approximately 81% of cough/cold ingredients were sold as OTC products and 19% were sold as prescription products.

3.2 OVER-THE-COUNTER COUGH/COLD PRODUCT SALES

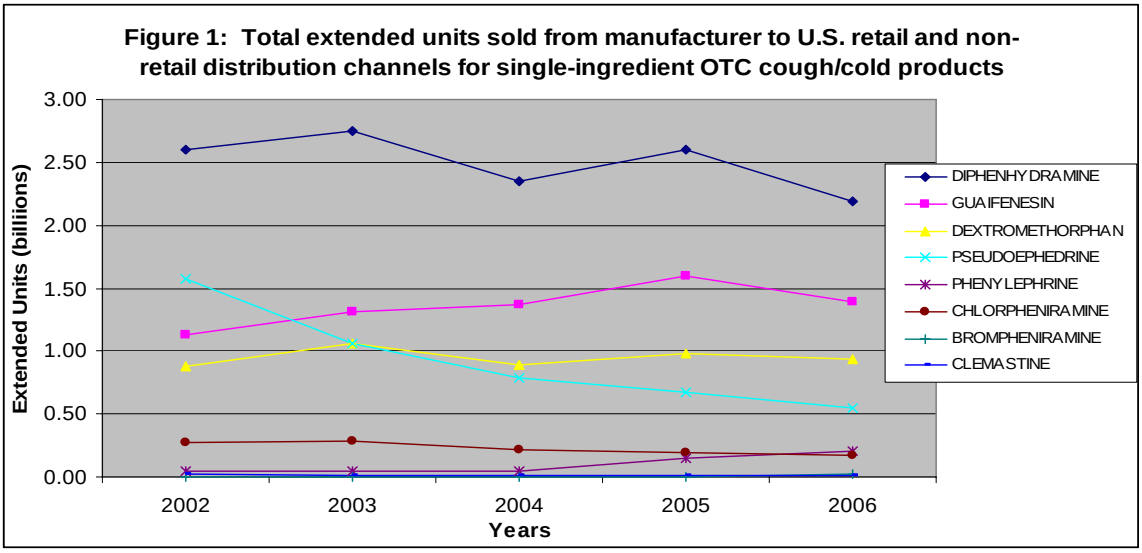
Of the OTC cough/cold market, the majority of cough/cold products are in multiple-ingredient/combination product formulations. Over the last 5 years, there has been an increase in the proportion of combination products sold in the OTC market, from approximately 75% in year 2002 to a high of 79% in year 2006 (Appendix 2: Table 1).

[1] Analysis of prescription usage by patient age was conduced for years 2002 through year 2005. Patient demographic factors are not available before year 2002 in Verispan, VONA.

3.2.1 OTC Single-Ingredient Product Sales

The proportion of sale of single-ingredient OTC cough/cold products remained relatively consistent for the years 2002 through 2006, excepting for pseudoephedrine and phenylephrine (Appendix 2: Table 2, Figure 1). Of the single-ingredient OTC product market, the most widely sold active ingredient over the last 5 years was diphenhydramine, accounting for nearly 40% of the single-ingredient market during the entire time surveyed. Guaifenesin was the second most common active ingredient-sold, followed by dextromethorphan, accounting for over a quarter and 17% of the single-ingredient OTC market during year 2006. Of these ingredients, the sale of pseudoephedrine took a dramatic decline (66% decrease) between years 2002 and 2006, going from nearly 1.6 billion extended units in sales in year 2002 to approximately 500 million extended units in year 2006. On the other hand, the sale of phenylephrine increased nearly 5-fold between those years, increasing from 41 million extended units sold in year 2002 to 206 million extended units sold in year 2006.

Figure 1: Total extended units sold from manufacturer to U.S. retail and non-retail distribution channels for single-ingredient OTC cough/cold products

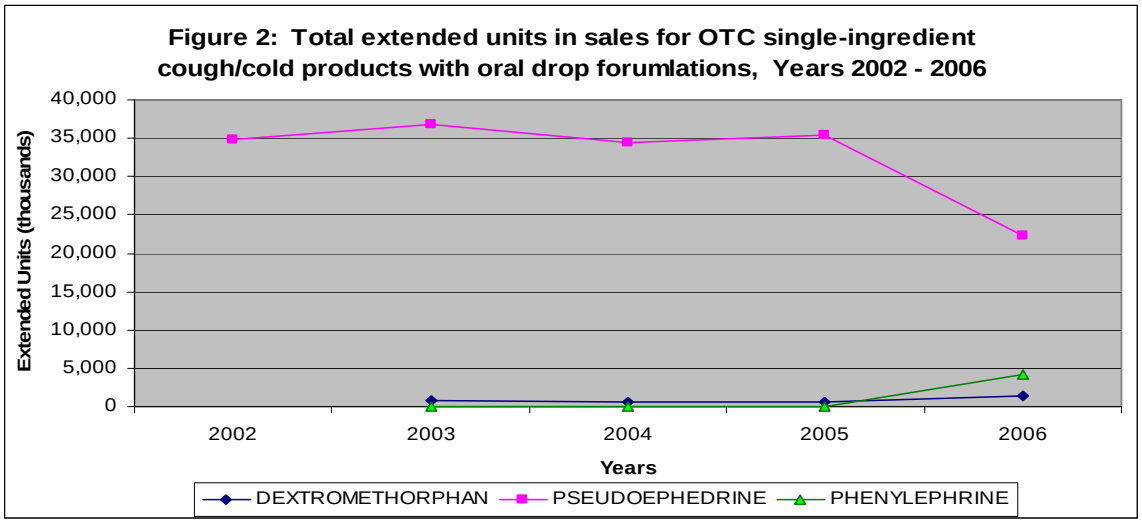


IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.

3.2.1.1 Dosage Forms - Liquid and Oral-Drop Formulations

During year 2006, the most common dosage form for guaifenesin and dextromethorphan is the systemic oral liquid, accounting for nearly 75% and 97% of sales for each, respectively (Appendix 2: Table 2). In addition, nearly 43% of diphenhydramine sales were for the systemic oral liquid dosage form. For the other cough/cold ingredients, pseudoephedrine, phenylephrine, chlorpheniramine, brompheniramine, and clemastine, the predominant dosage form was the systemic oral solid dosage forms. For phenylephrine products, nearly a quarter of sales were for the topical nasal and topical mouth/throat formulations.

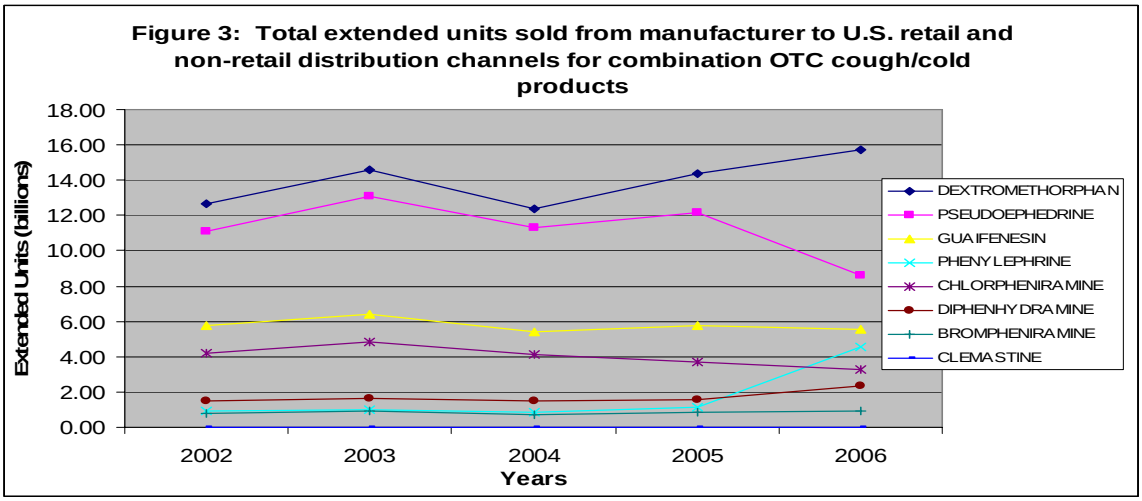
In order to ascertain use in the pediatric population, we evaluated the sale of oral drop formulations, assuming that only children under 2 years of age were consuming these formulations. Of the OTC single-ingredient cough/cold products, only dextromethorphan, pseudoephedrine, and phenylephrine had oral drop formulations (Figure 2, data not shown). Of the nearly 97% of liquid formulations of dextromethorphan, less than 1% were formulated as oral drop formulations in year 2006. For pseudoephedrine, approximately 20% of all liquid formulations (or 4% all single-ingredient pseudoephedrine) was formulated as oral drops. For phenylephrine, approximately 2% of all phenylephrine were formulated as oral drops.



IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.

3.2.2 Multiple-Ingredient/Combination

Multiple-ingredient or combination formulations of OTC cough/cold products make up the majority of OTC sales, accounting for nearly 80% of sales in year 2006 (Appendix 2: Table 1). Of these products, dextromethorphan was the most common active ingredient found in these products for the entire 5 years analyzed, accounting for nearly 67% to 75% of all OTC combination product sales (Appendix 2: Table 3, Figure 3). During year 2006, approximately 15.7 billion extended units (75%) of dextromethorphan were sold as combination OTC cough/cold products. Pseudoephedrine was the next most common active ingredient found in these cough/cold products, with nearly 59% to 62% of sales for all combination OTC cough/cold products during years 2002 to 2005. However, in year 2006, the sale of pseudoephedrine in these combination products declined dramatically, (29% decrease) from the previous year to make up only 41% of OTC combination cough/cold ingredients. The proportion of sales for the other cough/cold ingredients remained relatively steady during the 5 year-period surveyed, except for phenylephrine which increased nearly four-fold from year 2005 to 2006 to make up nearly 22% of overall sales for these OTC combination cough/cold products.

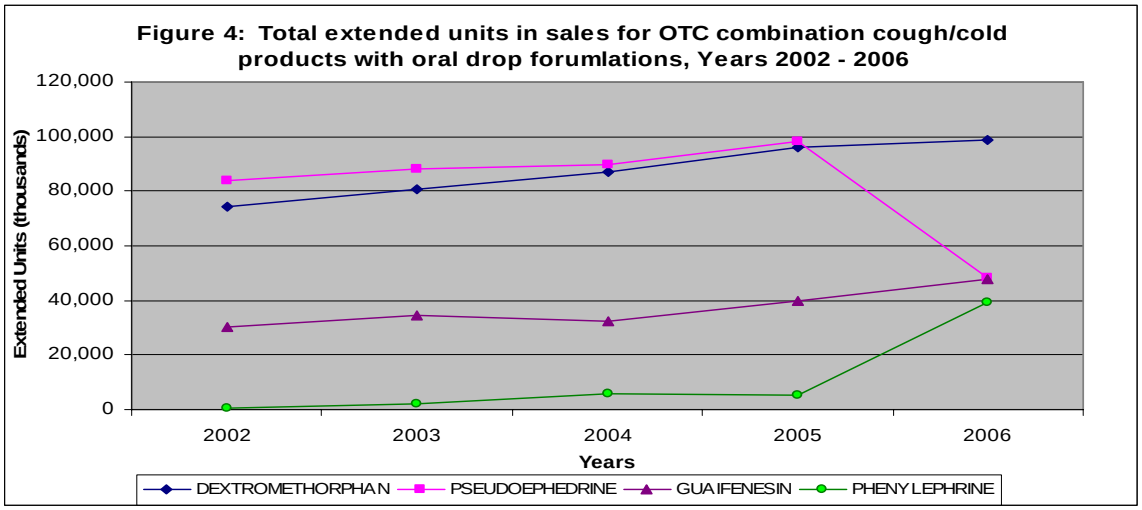


IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.

3.2.2.1 Dosage Forms - Liquid and Oral-Drop Formulations

Except for products containing diphenhydramine and clemastine, the most common dosage form sold for the combination OTC cough/cold products during year 2006 was the oral liquid dosage form (Appendix 2: Table 3). The most common dosage form sold for products containing diphenhydramine and clemastine were systemic oral solid dosage forms.

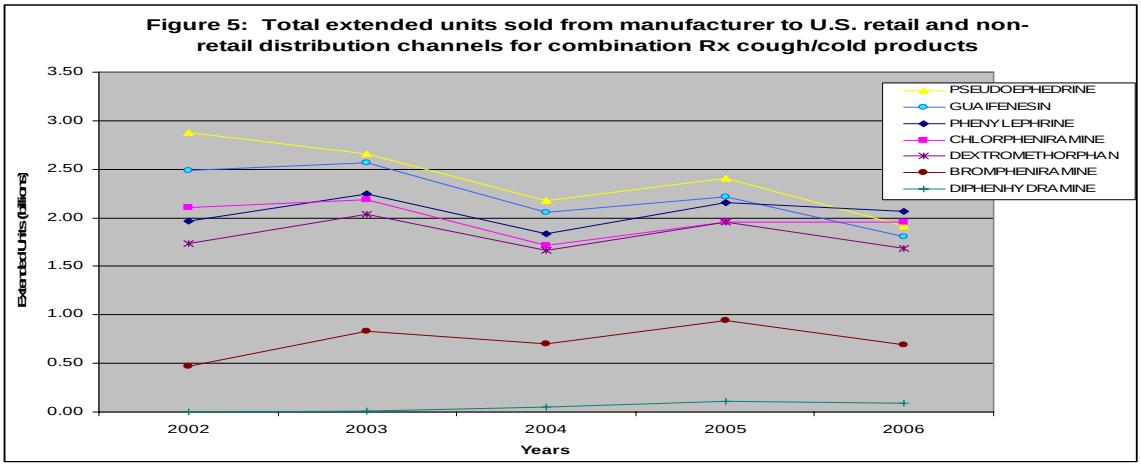
Assuming that only children under the age of 2 years are consuming oral drop formulations, less than 1% of all liquid dosage forms sold for dextromethorphan, pseudoephedrine, and guaifenesin were formulated as oral drop formulations during year 2006 (Figure 4, data not shown). For phenylephrine, a little over 1% of liquid dosage forms were formulated as oral drops. The sale of combination liquid oral drops products containing pseudoephedrine decreased by 50% since the previous year, whereas for phenylephrine, it increased by 7-fold (data not shown).



IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.

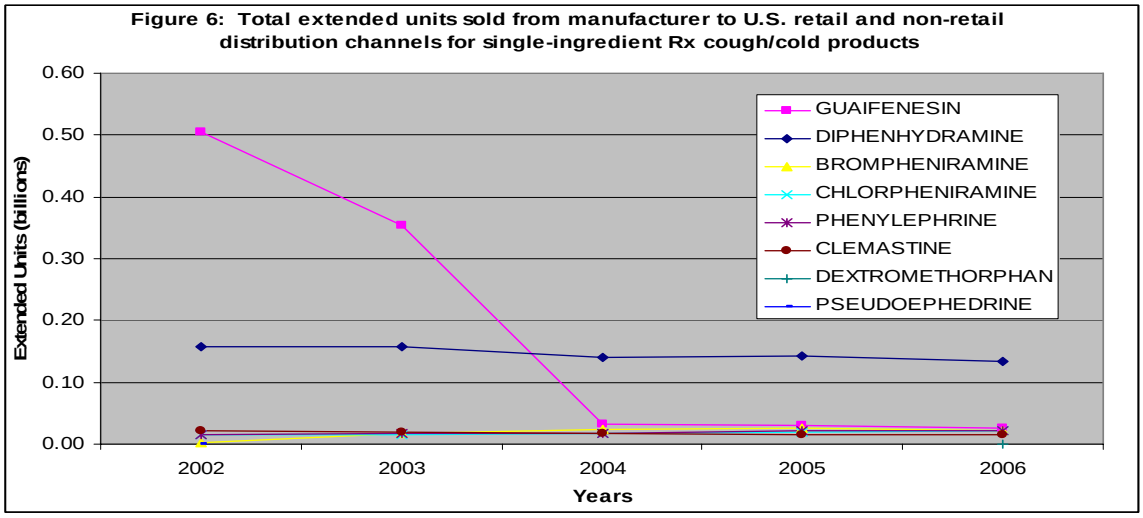
3.3 PRESCRIPTION COUGH/COLD PRODUCTS

In terms of total extended units sold, the sale of prescription combination cough/cold ingredients have fluctuated over the past 5 years, however, the proportion of sales for these ingredients have remained consistent throughout the years (Figure 5, data not shown).



IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.

For single-ingredient products, the number of extended units sold for guaifenesin products went from a high of 504 million extended units in year 2002 and plummeted to 32.9 million extended units in year 2004, and have remained at less than 7% of year 2002 volume since (Figure 6, data not shown).



IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.

3.3.1 Trends in Dispensed Prescriptions

The most commonly dispensed prescription cough/cold products in year 2006 were combination guaifenesin products, accounting for 29% (9.5 million dispensed prescriptions) of the cough/cold market share (Appendix 2: Table 4). This was followed by combination pseudoephedrine products, combination phenylephrine products, combination dextromethorphan-guaifenesin products, and combination chlorpheniramine products. Each accounted for approximately 20% (6.6 million dispensed prescription), 15% (~5 million dispensed prescriptions), 11% (3.4 million dispensed prescriptions), and 9% (3.0 million dispensed prescriptions), respectively, of the market share for the prescription cough/cold class during year 2006.

3.3.2 Patient Age

Cough/cold prescriptions dispensed to the 0-6 year age group accounted for approximately 3.9 million dispensed prescriptions or 12% of the entire cough/cold market in year 2006 (Appendix 2: Table 5). The most commonly dispensed cough/cold product in the pediatric age 0-6 years population was the phenylephrine combination products. These products accounted for nearly 1.5 million dispensed prescriptions or 39% of the entire market for the 0-6 year age group. The next most commonly dispensed cough/cold product was combination pseudoephedrine products with nearly 511 thousand prescriptions and 13% of the market. The product with the highest proportion of use in the pediatric population (0-6 years) were the combination pseudoephedrine-dextromethorphan products with over 97 thousand dispensed prescriptions out of a total of 142,200 prescriptions (69%) for all age groups.

3.3.3 Concurrent Use

Concurrent use of OTC medications cannot be captured using the available databases. Therefore, a truly reliable estimate of concurrent medication use with cough/cold products is not possible.

4 DISCUSSION

Findings from this drug use analysis should be interpreted in the context of the known limitations of the databases used. While demographic analyses are not possible with this database, pediatric use of cough/cold medications was estimated using this database with the assumption that only children under the age of 2 years old were consuming liquid oral drop formulations. The IMS Health, IMS National Sales Perspectives™ data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use. Furthermore, IMS estimates that approximately 50% of all U.S. OTC sales activity is captured in this database[2].

The dispensed prescription data provided by Verispan's Vector One®: National database captures retail prescription activity with a reasonable amount of certainty based on the large sample size of pharmacies and data projection methodology. However, data on OTC product use is not captured in this database. A reliable estimate of OTC product usage is not possible given the limitations of the drug usage databases available at the Agency's disposal. Unlike prescription transactions which capture detailed information on the drug product being dispensed as well as patient demographic data and prescribing specialty data, transactions for OTC products are not captured in the same method. Furthermore, the ease of accessibility for OTC products compared to prescription products and the PRN (as needed) nature of use make estimating OTC product usage difficult. For these reasons, the true extent of use for OTC products alone or in combination with other drug products is at best underestimated in this analysis.

5 CONCLUSIONS

The sale of OTC and prescription products containing cough/cold ingredients have fluctuated over the last 5 years, 2002 through 2006. The majority of cough/cold ingredients were sold as OTC products and only 19% were sold as prescription products.

Of the OTC cough/cold market, the majority of cough/cold products are in multiple-ingredient/combination product formulations. The proportion of sale of single-ingredient OTC cough/cold products remained relatively consistent for the years 2002 through 2006, except for pseudoephedrine and phenylephrine. Of the single-ingredient OTC product market, the most widely sold active ingredient over the last 5 years was diphenhydramine. For the multiple-ingredient/combination OTC cough/cold market, dextromethorphan was the most common active ingredient for the entire 5 years analyzed.

Assuming that only children under the age of 2 years are consuming oral drop formulations, less than 1% of all liquid dosage forms sold for dextromethorphan, pseudoephedrine, phenylephrine, and guaifenesin were formulated as oral drop formulations during year 2006 for both single-ingredient and combination cough/cold products.

The most commonly dispensed prescription cough/cold products in year 2006 were combination guaifenesin products, accounting for 29% (9.5 million dispensed prescriptions) of the cough/cold market share. Cough/cold prescriptions dispensed to the 0-6 year age group accounted for approximately 3.9 million dispensed prescriptions or 12% of the entire cough/cold market in year

[2] IMS Health, IMS National Sales Perspectives™ Retail and Non-Retail Sample Coverage of the Universe (09/15/06).

2006. The most commonly dispensed cough/cold product in the pediatric age 0-6 years population was the phenylephrine combination products. Concurrent use of OTC medications cannot be captured using the available databases. Therefore, a truly reliable estimate of concurrent medication use with cough/cold products is not possible.

APPENDICES

Appendix 1: Data Source

Outpatient Drug Usage

IMS HEALTH

IMS Health, IMS National Sales Perspectives™

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

VERISPAN, LLC

Vector One®: National (VONA)

Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims yearly, representing over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

Appendix 2: Table and figures

Table 1: Sale of OTC and prescription (Rx) products containing selected cough/cold ingredients sold from manufacturers to retail† and non-retail‡ channels of distribution from year 2002 through 2006.

	Extended Units* (in thousands), %									
	2002		2003		2004		2005		2006	
Rx and OTC Market	33,731,812	*100.0%*	36,458,013	*100.0%*	30,508,235	*100.0%*	33,666,154	*100.0%*	32,889,112	*100.0%*
OTC	25,565,058	*75.8%*	28,195,559	*77.3%*	23,993,295	*78.6%*	26,254,729	*78%*	26,545,840	*80.7%*
Combination	19,042,237	*74.5%*	21,673,730	*76.9%*	18,324,427	*76.4%*	20,053,922	*76.4%*	21,077,738	*79.4%*
Single-Ingredient	6,522,820	*25.5%*	6,521,829	*23.1%*	5,668,868	*23.6%*	6,200,807	*23.6%*	5,468,102	*20.6%*
Rx	8,154,048	*24.2%*	8,229,939	*22.6%*	6,484,934	*21.3%*	7,387,971	*21.9%*	6,333,897	*19.3%*
Combination	7,437,129	*91.2%*	7,650,352	*93%*	6,237,152	*96.2%*	7,133,734	*96.6%*	6,094,042	*96.2%*
Single-Ingredient	716,919	*8.8%*	579,588	*7%*	247,782	*3.8%*	254,237	*3.4%*	239,855	*3.8%*

IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.
* Extended Units – tablets, capsules, millimeters of solution.
† **Retail** channels include chain, independent, foodstore, mail order, discount houses, and mass merchandiser pharmacies in the entire United States. .
‡ **Non-retail** channels include hospitals, long-term care facilities, clinics, home health care providers, and HMOs in the entire United States.
Figures do not sum to total due to products categorized as "Status Unknown" not shown.

Table 2: Sale of single-ingredient OTC cough/cold products by dosage form from year 2002 through 2006.

	Extended Units* (in thousands), %									
	2002		2003		2004		2005		2006	
Single-Ingredient OTC cough/cold	6,522,820	*100.0%*	6,521,829	*100.0%*	5,668,868	*100.0%*	6,200,807	*100.0%*	5,468,102	*100.0%*
DIPHENHYDRAMINE	2,604,956	*39.9%*	2,746,320	*42.1%*	2,352,472	*41.5%*	2,600,820	*41.9%*	2,185,662	*40.0%*
SYSTEMIC ORAL LIQUID	1,578,909	*60.6%*	1,666,138	*60.7%*	1,331,470	*56.6%*	1,374,688	*52.9%*	936,209	*42.8%*
SYSTEMIC ORAL SOLID REG	667,631	*25.6%*	695,473	*25.3%*	683,430	*29.1%*	896,554	*34.5%*	913,667	*41.8%*
TOPICAL DERMATOLOGICALS	358,416	*13.8%*	384,710	*14.0%*	336,827	*14.3%*	329,540	*12.7%*	333,951	*15.3%*
MOUTH/THROAT TOPICAL		*0%*		*0%*	745	*0%*	38	*0%*	1,835	*0.1%*
GUAIFENESIN	1,123,870	*17.2%*	1,306,865	*20.0%*	1,364,886	*24.1%*	1,596,722	*25.8%*	1,388,086	*25.4%*
SYSTEMIC ORAL LIQUID	1,104,106	*98.2%*	1,229,375	*94.1%*	1,089,868	*79.9%*	1,234,456	*77.3%*	1,037,554	*74.7%*
SYSTEMIC ORAL SOLID L/A	2,186	*0.2%*	65,031	*5.0%*	238,595	*17.5%*	324,659	*20.3%*	280,715	*20.2%*
SYSTEMIC ORAL SOLID REG	17,579	*1.6%*	12,459	*1%*	36,423	*2.7%*	37,607	*2.4%*	69,817	*5.0%*
DEXTROMETHORPHAN	877,673	*13.5%*	1,060,314	*16.3%*	893,591	*15.8%*	976,153	*15.7%*	937,843	*17.2%*
SYSTEMIC ORAL LIQUID	730,665	*83.3%*	901,064	*85.0%*	763,385	*85.4%*	939,162	*96.2%*	909,935	*97.0%*
SYSTEMIC ORAL SOLID REG	2,317	*0.3%*	19,061	*1.8%*	18,457	*2.1%*	18,368	*1.9%*	19,334	*2.1%*
MOUTH/THROAT TOPICAL	144,691	*16.5%*	140,189	*13.2%*	111,749	*12.5%*	18,622	*1.9%*	8,574	*0.9%*
PSEUDOEPHEDRINE	1,577,978	*24.2%*	1,065,629	*16.3%*	785,710	*13.9%*	671,383	*10.8%*	542,729	*9.9%*
SYSTEMIC ORAL SOLID REG	1,332,107	*84.4%*	762,523	*71.6%*	517,851	*65.9%*	445,792	*66.4%*	369,486	*68.1%*
SYSTEMIC ORAL LIQUID	197,683	*12.5%*	252,006	*23.6%*	209,642	*26.7%*	168,470	*25.1%*	113,754	*21.0%*
SYSTEMIC ORAL SOLID L/A	48,188	*3.1%*	51,100	*4.8%*	58,216	*7.4%*	57,121	*8.5%*	59,489	*11.0%*
PHENYLEPHRINE	41,342	*0.6%*	41,983	*0.6%*	41,181	*0.7%*	152,098	*2.5%*	206,310	*3.8%*
SYSTEMIC ORAL SOLID REG	15	*0%*	62	*0.1%*	61	*0.1%*	113,344	*74.5%*	153,930	*74.6%*
TOPICAL NASAL	41,269	*99.8%*	41,837	*99.7%*	41,047	*99.7%*	38,736	*25.5%*	33,297	*16.1%*
MOUTH/THROAT TOPICAL		*0%*		*0%*		*0%*		*0%*	14,997	*7.3%*
SYSTEMIC ORAL LIQUID		*0%*	70	*0.2%*	73	*0.2%*	18	*0%*	4,086	*2%*
TOPICAL OPHTHALMIC	59	*0.1%*	14	*0%*	0	*0%*		*0%*		*0%*
CHLORPHENIRAMINE	278,076	*4.3%*	288,089	*4.4%*	221,316	*3.9%*	189,222	*3.1%*	176,211	*3.2%*
SYSTEMIC ORAL SOLID REG	248,124	*89.2%*	262,475	*91.1%*	212,456	*96.0%*	184,774	*97.6%*	163,768	*92.9%*
SYSTEMIC ORAL SOLID L/A	24,729	*8.9%*	23,173	*8%*	7,145	*3.2%*	3,110	*1.6%*	11,389	*6.5%*
SYSTEMIC ORAL LIQUID	5,223	*1.9%*	2,441	*0.8%*	1,715	*0.8%*	1,339	*0.7%*	1,054	*0.6%*

BROMPHENIRAMINE	504	*0%*	391	*0%*	207	*0%*	26	*0%*	21,502	*0.4%*
SYSTEMIC ORAL LIQUID	209	*41.5%*	233	*59.6%*	143	*69.1%*	26	*100.0%*	21,502	*100.0%*
SYSTEMIC ORAL SOLID REG	295	*58.5%*	158	*40.4%*	64	*30.9%*		*0%*		*0%*
CLEMASTINE	18,422	*0.3%*	12,238	*0.2%*	9,507	*0.2%*	14,383	*0.2%*	9,760	*0.2%*
SYSTEMIC ORAL SOLID REG	18,422	*100.0%*	12,236	*100.0%*	9,381	*98.7%*	11,363	*79.0%*	9,048	*92.7%*
SYSTEMIC ORAL SOLID L/A		*0%*	3	*0%*	125	*1.3%*	3,019	*21.0%*	712	*7.3%*

IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.
* Extended Units – tablets, capsules, millimeters of solution.
Figures do not sum to total due to products categorized as “Status Unknown” not shown.

Table 3: Sale of combination OTC cough/cold products by dosage form from year 2002 through 2006.

	Extended Units* (in thousands), %									
	2002		2003		2004		2005		2006	
COMBINATION	19,042,237	*100.0%*	21,673,730	*100.0%*	18,324,427	*100.0%*	20,053,922	*100.0%*	21,077,738	*100.0%*
DEXTROMETHORPHAN	12,673,861	*66.6%*	14,569,225	*67.2%*	12,384,783	*67.6%*	14,376,022	*71.7%*	15,739,997	*74.7%*
SYSTEMIC ORAL LIQUID	11,867,926	*93.6%*	13,677,683	*93.9%*	11,628,320	*93.9%*	13,515,770	*94.0%*	14,850,013	*94.3%*
SYSTEMIC ORAL SOLID REG	798,060	*6.3%*	883,613	*6.1%*	729,584	*5.9%*	762,841	*5.3%*	760,063	*4.8%*
SYSTEMIC ORAL SOLID L/A		*0.0%*		*0.0%*	18,961	*0.2%*	96,711	*0.7%*	106,817	*0.7%*
MOUTH/THROAT TOPICAL	7,876	*0.1%*	7,929	*0.1%*	7,917	*0.1%*	191	*0.0%*	22,470	*0.1%*
SYSTEMIC ALL OTHERS		*0.0%*		*0.0%*		*0.0%*	510	*0.0%*	634	*0.0%*
PSEUDOEPHEDRINE	11,130,997	*58.5%*	13,058,061	*60.2%*	11,316,369	*61.8%*	12,194,673	*60.8%*	8,615,169	*40.9%*
SYSTEMIC ORAL LIQUID	7,324,497	*65.8%*	8,729,988	*66.9%*	7,627,180	*67.4%*	8,965,051	*73.5%*	6,879,479	*79.9%*
SYSTEMIC ORAL SOLID REG	3,771,718	*33.9%*	4,228,361	*32.4%*	3,595,748	*31.8%*	3,123,112	*25.6%*	1,580,160	*18.3%*
SYSTEMIC ORAL SOLID L/A	34,782	*0.3%*	99,711	*0.8%*	93,442	*0.8%*	106,000	*0.9%*	154,897	*1.8%*
SYSTEMIC ALL OTHERS	0	*0.0%*		*0.0%*		*0.0%*	510	*0.0%*	634	*0.0%*
GUAIFENESIN	5,731,498	*30.1%*	6,389,651	*29.5%*	5,380,120	*29.4%*	5,733,963	*28.6%*	5,583,771	*26.5%*
SYSTEMIC ORAL LIQUID	5,460,927	*95.3%*	6,089,914	*95.3%*	5,092,205	*94.6%*	5,331,400	*93.0%*	5,064,273	*90.7%*
SYSTEMIC ORAL SOLID REG	270,570	*4.7%*	299,737	*4.7%*	268,953	*5.0%*	291,999	*5.1%*	353,305	*6.3%*
SYSTEMIC ORAL SOLID L/A		*0.0%*		*0.0%*	18,961	*0.4%*	110,564	*1.9%*	166,194	*3.0%*
PHENYLEPHRINE	957,815	*5.0%*	1,031,551	*4.8%*	846,685	*4.6%*	1,136,746	*5.7%*	4,545,127	*21.6%*
SYSTEMIC ORAL LIQUID	677,395	*70.7%*	753,357	*73.0%*	593,188	*70.1%*	839,411	*73.8%*	3,705,708	*81.5%*
SYSTEMIC ORAL SOLID REG	231,179	*24.1%*	231,232	*22.4%*	220,278	*26.0%*	260,638	*22.9%*	779,846	*17.2%*
TOPICAL NASAL	46,361	*4.8%*	44,416	*4.3%*	30,887	*3.6%*	34,851	*3.1%*	34,995	*0.8%*
MOUTH/THROAT TOPICAL		*0.0%*		*0.0%*		*0.0%*		*0.0%*	22,470	*0.5%*
TOPICAL OPHTHALMIC	2,220	*0.2%*	2,057	*0.2%*	1,849	*0.2%*	1,420	*0.1%*	1,749	*0.0%*
TOPICAL RECTAL	661	*0.1%*	488	*0.0%*	484	*0.1%*	426	*0.0%*	359	*0.0%*
SYSTEMIC ORAL SOLID L/A	0	*0.0%*		*0.0%*		*0.0%*		*0.0%*		*0.0%*
CHLORPHENIRAMINE	4,197,956	*22.0%*	4,866,230	*22.5%*	4,107,751	*22.4%*	3,723,089	*18.6%*	3,296,187	*15.6%*
SYSTEMIC ORAL LIQUID	1,550,874	*36.9%*	1,763,312	*36.2%*	1,396,827	*34.0%*	1,571,132	*42.2%*	2,137,926	*64.9%*
SYSTEMIC ORAL SOLID REG	2,638,430	*62.9%*	3,092,935	*63.6%*	2,707,174	*65.9%*	2,151,926	*57.8%*	1,158,251	*35.1%*
TOPICAL DERMATOLOGICALS	18	*0.0%*	72	*0.0%*	59	*0.0%*	30	*0.0%*	10	*0.0%*
SYSTEMIC ORAL SOLID L/A	8,634	*0.2%*	9,911	*0.2%*	3,690	*0.1%*	0	*0.0%*		*0.0%*

SYSTEMIC ALL OTHERS	0	*0.0%*		*0.0%*		*0.0%*		*0.0%*		*0.0%*
DIPHENHYDRAMINE	1,501,655	*7.9%*	1,618,973	*7.5%*	1,489,905	*8.1%*	1,578,620	*7.9%*	2,318,085	*11.0%*
SYSTEMIC ORAL SOLID REG	1,313,735	*87.5%*	1,393,001	*86.0%*	1,271,934	*85.4%*	1,292,871	*81.9%*	1,378,660	*59.5%*
SYSTEMIC ORAL LIQUID	94,244	*6.3%*	103,187	*6.4%*	104,161	*7.0%*	160,536	*10.2%*	828,656	*35.7%*
TOPICAL DERMATOLOGICALS	93,676	*6.2%*	122,785	*7.6%*	113,810	*7.6%*	125,214	*7.9%*	110,769	*4.8%*
BROMPHENIRAMINE	798,199	*4.2%*	917,058	*4.2%*	716,043	*3.9%*	883,477	*4.4%*	892,373	*4.2%*
SYSTEMIC ORAL LIQUID	784,863	*98.3%*	907,383	*98.9%*	710,059	*99.2%*	880,627	*99.7%*	888,440	*99.6%*
SYSTEMIC ORAL SOLID REG	14,139	*1.8%*	10,317	*1.1%*	6,585	*0.9%*	3,338	*0.4%*	4,495	*0.5%*
SYSTEMIC ORAL SOLID L/A	24,838	*3.1%*	22,761	*2.5%*	23,303	*3.3%*	21,561	*2.4%*	22,653	*2.5%*
CLEMASTINE	22,827	*0.1%*	17,617	*0.1%*	9,347	*0.1%*	3,650	*0.0%*	9	*0.0%*
SYSTEMIC ORAL SOLID L/A	2,200	*9.6%*	22	*0.1%*	10	*0.1%*	32	*0.9%*	6	*59.6%*
SYSTEMIC ORAL SOLID REG	20,627	*90.4%*	17,595	*99.9%*	9,337	*99.9%*	3,617	*99.1%*	4	*40.4%*
SYSTEMIC ALL OTHERS	0	*100.0%*		*0.0%*		*0.0%*		*0.0%*		*0.0%*

IMS Health, IMS National Sales Perspectives™, Years 2002 – 2006; Source file: 0707cc01.dvr.
* Extended Units – tablets, capsules, millimeters of solution.
Figures do not sum to total since to more than one ingredient may be combined with another.

Table 4: Total dispensed prescriptions for cough/cold products during year 2006

	2006	
	Retail TRxs	**Share**
	N	***%***
TOTAL	32,813,605	*100.0%*
GUIFEN COMBO	9,528,602	*29.0%*
PSEUDOEPHEDRIN COMBO	6,586,523	*20.1%*
PHENYLEPHRINE COMBO	4,993,515	*15.2%*
DM-GUAIFEN	3,436,251	*10.5%*
CHLORPHENIRAMINE COMBO	3,016,440	*9.2%*
DIPHENHYDRAMINE PLAIN	1,908,357	*5.8%*
PSE-CHLORPHENIRAMINE	1,551,996	*4.7%*
PSEUDOEPHEDRINE PLAIN	436,144	*1.3%*
PSE-GUAI	288,373	*0.9%*
CHLORPHENIRAMINE PLAIN	259,951	*0.8%*
GUAIFENESIN PLAIN	250,765	*0.8%*
BROMPHENIRAMINE PLAIN	226,469	*0.7%*
PSE-DM COMBO	142,200	*0.4%*
CLEMASTINE	119,415	*0.4%*
PHENYLEPHRINE PLAIN	35,501	*0.1%*
DEXTROMETHORPHAN HBr	15,465	*0.0%*
BROMPHENIRAMINE/PE	11,863	*0.0%*
DIPHENHYDRAMINE COMBO	5,762	*0.0%*
DEXTROMETHORPHAN/PPA	13	*0.0%*

Verispan, VONA: Years 2002 – 2006, Extracted July 2007. Source file: VONA 2007-1022 cough cold combo2 TRx age

Table 5: Total number of dispensed prescriptions for cough/cold products in the pediatric age group 0-6 years for years 2002 - 2006

	2002		2003		2004		2005		2006	
	Retail TRxs	*Share**	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET All Ages	**46,987,187**	***100.0%***	**45,550,316**	***100.0%***	**35,622,214**	***100.0%***	**37,588,737**	***100.0%***	**32,813,605**	***100.0%***
All age 0-6	**4,945,724**	***10.5%***	**4,463,838**	***9.8%***	**3,951,508**	***11.1%***	**4,027,748**	***10.7%***	**3,868,884**	***11.8%***
CHLORPHENIRAMINE PLAIN	8,688	*5.6%*	6,052	*4.1%*	5,178	*3.4%*	7,972	*4.4%*	24,855	*9.6%*
CHLORPHENIRAMINE COMBO	46,177	*1.6%*	55,094	*1.8%*	41,814	*1.5%*	41,751	*1.3%*	55,735	*1.8%*
PSE-CHLORPHENIRAMINE	251,180	*15.7%*	71,479	*4.7%*	62,634	*4.3%*	94,811	*5.7%*	90,077	*5.8%*
PSEUDOEPHEDRINE PLAIN	119,335	*25.3%*	98,164	*22.1%*	72,206	*20.1%*	73,876	*18.6%*	57,810	*13.3%*
PSE-GUAI	164,721	*62.2%*	138,477	*46.4%*	119,020	*43.2%*	138,010	*43.5%*	145,181	*50.3%*
PSEUDOEPHEDRIN COMBO	1,536,476	*11.7%*	1,217,973	*10.4%*	863,057	*9.9%*	649,677	*7.9%*	510,683	*7.8%*
PSE-DM COMBO	0		1,455	*71.6%*	15,069	*70.8%*	90,288	*68.6%*	97,376	*68.5%*
DEXTROMETHORPHAN HBr	11,467	*35.9%*	11,219	*37.4%*	9,609	*37.4%*	10,115	*37.7%*	6,208	*40.1%*
DM-GUAIFEN	335,460	*7.8%*	358,505	*7.3%*	447,757	*10.4%*	459,339	*10.1%*	464,005	*13.5%*
DEXTROMETHORPHAN/PPA	720	*77.5%*	69	*69.0%*	8	*72.7%*	7	*36.8%*	3	*23.1%*
DIPHENHYDRAMINE PLAIN	432,441	*17.9%*	409,595	*18.7%*	413,548	*18.9%*	480,303	*22.5%*	372,755	*19.5%*
DIPHENHYDRAMINE COMBO	0		0		0		0		1,161	*20.1%*
PHENYLEPHRINE PLAIN	10,184	*32.1%*	9,804	*32.6%*	8,750	*34.2%*	19,595	*44.4%*	13,699	*38.6%*
PHENYLEPHRINE COMBO	1,373,790	*33.5%*	1,340,421	*30.5%*	1,269,153	*29.9%*	1,325,186	*26.0%*	1,493,313	*29.9%*
GUAIFENESIN PLAIN	40,002	*0.5%*	25,626	*0.4%*	15,269	*2.8%*	27,341	*6.5%*	36,584	*14.6%*
GUIFEN COMBO	551,556	*5.8%*	596,189	*5.8%*	474,887	*4.6%*	479,046	*4.4%*	406,199	*4.3%*
CLEMASTINE	60,429	*40.1%*	48,995	*34.2%*	42,143	*30.3%*	35,761	*26.9%*	21,613	*18.1%*
BROMPHENIRAMINE PLAIN	3,098	*68.7%*	74,721	*58.8%*	91,406	*53.3%*	94,670	*39.9%*	71,627	*31.6%*
BROMPHENIRAMINE/PE	0		0		0		0		8,107	*68.3%*

Verispan, VONA: Years 2002 – 2006, Extracted July 2007. Source file: VONA 2007-1022 cough cold combo2 TRx age.qry
*Percent share based on dispensed prescriptions for age 0-6 years divided by of total dispensed prescriptions for drug group from Table 4.

Appendix 3: Prescription Cough/Cold Products List

Group Molecule:

DIPHENHYDRAMINE PLAIN

diphenhydramine hcl, diphenhydramine hcl, diphenhydramine hcl, diphenhydramine hcl, diphenhydramine hcl, diphenhydramine hcl, diphenhydramine tannate

DIPHENHYDRAMINE COMBO

diphenhy hcl/phenyleph hcl tan, diphenhy hcl/phenyleph hcl tan, diphenhyd hcl/p ephrin hcl tan, diphenhyd tan/carbetapen tan, diphenhyd tan/phenylep tan, diphenhydramine hcl/calamine, diphenhydramine hcl/niacin, diphenhydramine hcl/phenyl, diphenhydramine hcl/zinc oxide, diphenhydramine/carbetapen tan

PHENYLEPHRINE PLAIN

phenylephrine hcl, phenylephrine hcl, phenylephrine hcl, phenylephrine hcl, phenylephrine hcl, phenylephrine hcl, phenylephrine tannate

PHENYLEPHRINE COMBO

carbinoxamine & phenylephrine, phenylep tan/pyrila tan/d-meth, phenyleph cpm w/ hydroco, phenyleph cpm w/ hydroco/gg, phenyleph cpm w/ hydrocod, phenyleph hcl/pyril mal/dm hbr, phenyleph tan/brom tan/d-meth, phenyleph tan/brom tan/d-meth, phenyleph/brom/m hydroco/b tan, phenyleph/chlor-mal/scop, phenyleph/cpm/bellad alk, phenyleph/dchlor/hydroco tan, phenyleph/diphenhy/d-meth tan, phenyleph/guaifen/homopath prd, phenyleph/hydrocodone/pyril, phenylephr/dp-hydram/hcod tan, phenylephrin/dbromphen/hydroco, phenylephrin/dexchlor/pyril dm, phenylephrine hcl/antipyrine, phenylephrine hcl/carbinox mal, phenylephrine hcl/carbinox mal, phenylephrine hcl/chlor-mal, phenylephrine hcl/chlor-mal, phenylephrine hcl/hydrocodone, phenylephrine hcl/phenir, phenylephrine hcl/phenir, phenylephrine hcl/phenylprop, phenylephrine hcl/pyrilamine, phenylephrine hcl/pyrilamine, phenylephrine hcl/pyrilamine, phenylephrine hcl/pyrilamine, phenylephrine hcl/scopolamine, phenylephrine hcl/zinc sulfate, phenylephrine hydrochloride, phenylephrine tan/pyrilamine, phenylephrine tan/pyrilamine, phenylephrine w/hydrocodone/gg, phenylephrine/antipy/b-caine, phenylephrine/apap/chlorphenir, phenylephrine/apap/chlorphenir, phenylephrine/apap/p-tlox/cp, phenylephrine/apap/pyril/cpm, phenylephrine/br-phenir, phenylephrine/br-phenir, phenylephrine/br-phenir, phenylephrine/bromphen/carbeta, phenylephrine/brompheniram dm, phenylephrine/brompheniramin, phenylephrine/brompheniramin, phenylephrine/brompheniramin, phenylephrine/carbetapen tan, phenylephrine/carbetapen tan, phenylephrine/carbetapen/guai, phenylephrine/carbetapen/guai, phenylephrine/carbinox dm, phenylephrine/chlor-mal/scop, phenylephrine/chlor-mal/scop, phenylephrine/chlor-tan, phenylephrine/chlor-tan, phenylephrine/chlorphen/dm, phenylephrine/chlorphen/dm/gg, phenylephrine/chlorphenir, phenylephrine/chlorphenir, phenylephrine/chlorphenir, phenylephrine/chlorphenir, phenylephrine/cod/promethazine, phenylephrine/cod/pyrilamine, phenylephrine/cpmm/bellad alk, phenylephrine/cyclopentolate, phenylephrine/dexbromphen/hcod, phenylephrine/dhcodeine bt/cp, phenylephrine/dhcodeine bt/cp, phenylephrine/dihy-cod/cpm, phenylephrine/dm/gg, phenylephrine/dm/gg, phenylephrine/dm/gg/w/apap, phenylephrine/dp-hydram tan, phenylephrine/dp-hydram tan, phenylephrine/guaifenesin, phenylephrine/guaifenesin, phenylephrine/hcod bt/carbinox, phenylephrine/hcod bt/carbinox, phenylephrine/hcod bt/pyril/cp, phenylephrine/hcod tan/dpha, phenylephrine/hydrocodone/bpm, phenylephrine/hydrocodone/bpm, phenylephrine/hydrocodone/cp, phenylephrine/hydrocodone/d-cp, phenylephrine/hydrocodone/dpha, phenylephrine/hydrocodone/pyr, phenylephrine/p-tlox ci/cp,

phenylephrine/p-tlox ci/cp, phenylephrine/p-tlox ci/cp, phenylephrine/ppa/dihy-cod/cpm, phenylephrine/promethazine, phenylephrine/pyril mal/cp, phenylephrine/pyril mal/cp, phenylephrine/pyril tan, phenylephrine/pyril tan, phenylephrine/pyril tan/cp, phenylephrine/pyrilamine dm, phenylephrine/pyrilamine/cpm, phenylephrine/pyrilamine/cpm, phenylephrine/sal-amide/cp, phenylephrine/thenyldiamine, phenyleprhine/chlor-mal/scop

PSEUDOEPHEDRINE PLAIN

pseudoephedrine hcl, pseudoephedrine hcl, pseudoephedrine hcl

PSEUDOEPHEDRINE COMBO

carbinox tan/pseudo tan, carbinoxamine & pseudoeph, guaifenesin/p-ephed hcl, guaifenesin/p-ephed hcl, guaifenesin/p-ephed hcl/cod, guaifenesin/p-ephed hcl/hcod, guaifenesin/p-ephed/cod, guaifenesin/p-ephed/hcod/cpm, guaifenesin/p-ephedrine/bpm, guaifenesin/p-ephedrine/cod, guaifenesin/p-ephedrine/cod, guaifenesin/p-ephedrine/cod, guaifenesin/p-ephedrine/cod, guaifenesin/p-ephedrine/hcod, guaifenesin/p-ephedrine/hcod, guaifenesin/pseudoephedrine, guaifenesin/pseudoephedrine, guaifenesin/pseudoephedrine, guaifenesin/pseudoephedrine, guaifenesin/pseudoephedrine, guaifenesin/pseudophedrine, guaifenesin/psuedoephedrine, pse methscopol/cpm methscopol, pseudo hcl/carb mal/dm hbr tan, pseudo tan/brom tan/d-meth tan, pseudo tan/carb tan/d-meth tan, pseudo tan/carb tan/d-meth tan, pseudo tan/chlor tan/dm tan, pseudo tan/dechlor tan/dm tan, pseudo tan/dechlor tan/dm tan, pseudoeph/bromphen/hydroco, pseudoephd tan/dexchlor tan/dm, pseudoephdrine/carbinox, pseudoephed/bromphen/dm, pseudoephed/carbinox/dm, pseudoephedrine hcl/acrivas, pseudoephedrine hcl/codeine, pseudoephedrine hcl/triprol, pseudoephedrine hcl/triprol, pseudoephedrine sulfate, pseudoephedrine sulfate/azata, pseudoephedrine tan/chlor-tan, pseudoephedrine w/ dm-gg, pseudoephedrine w/ dm/gg, pseudoephedrine w/ dm/gg, pseudoephedrine/acetaminophen, pseudoephedrine/apap/caffein, pseudoephedrine/asa/caffein, pseudoephedrine/aspirin, pseudoephedrine/br-phenir, pseudoephedrine/br-phenir, pseudoephedrine/carbinox, pseudoephedrine/carbinox, pseudoephedrine/carbinox, pseudoephedrine/chlorcyclizine, pseudoephedrine/cod/triprol, pseudoephedrine/cod/triprol, pseudoephedrine/d-bromphenir, pseudoephedrine/d-bromphenir, pseudoephedrine/dp-hydramine, pseudoephedrine/guaifenesin, pseudoephedrine/guaifenesin, pseudoephedrine/hydrocodone, pseudoephedrine/promethazine, psuedoephedrine/carbinox

CHLORPHENIRAMINE PLAIN

chlorpheniramine maleate, chlorpheniramine maleate, chlorpheniramine maleate, chlorpheniramine maleate, chlorpheniramine tannate, chlorpheniramine tannate, chlorpheniramine tannate, chlorpheniramine tannate

CHLORPHENIRAMINE COMBO

chlorphen tan/pheny tan/m-scop, chlorphen tan/pyril tan/pe tan, chlorphen/phenyltolox/pe, chlorphen/pyril/phenyleph tan, chlorphenir tan/phenyleph tan, chlorphenir/me-scop0lamine, chlorphenir/me-scop0lamine, chlorphenir/me-scop0lamine, chlorpheniramine maleate/epi, chlorpheniramine/hydrocodone, chlorpheniramine/phenyl/m-scop, chlorpheniramine/phenylephrine, chlorpheniramn/hydrocodone tan

CLEMASTINE

clemastine fumarate, clemastine fumarate

BROMPHENIRAMINE PLAIN

brompheniramine maleate, brompheniramine maleate, brompheniramine maleate, brompheniramine maleate, brompheniramine maleate, brompheniramine tannate, brompheniramine tannate

BROMPHENIRAMINE/PE

bromphen mal/phenyl hcl tann, bromphenir tan/phenyleph tan

DM-GUAIFEN

guaifen/d-methorph/p-ephed/bpm, guaifen/d-methorphan hb pe, guaifen/d-methorphan hb/bpm, guaifen/d-methorphan hb/k cit, guaifen/d-methorphan hb/pe, guaifen/d-methorphan hb/pe/bpm, guaifen/d-methorphan hb/pe/cp, guaifen/d-methorphan/ipec, guaifen/d-methorphan/k cit, guaifen/d-methorphan/p-ephed, guaifen/d-methorphan/p-ephed, guaifen/d-methorphan/p-ephed, guaifen/d-methorphan/pe/apap, guaifen/d-methorphan/pe/apap, guaifen/d-methorphan/pe/cpm, guaifen/d-methorphan/pe/ppa, guaifen/d-methorphan/ppa, guaifen/d-methrophan hb/pe, guaifen/dm hb/p-ephedrine, guaifen/dm hb/p-ephedrine/apap, guaifen/dm hb/p-ephedrine/bpm, guaifen/dm hb/phenyleph/d-bp, guaifen/dm/p-ephedrine, guaifen/dm/p-ephedrine/dexbrom, guaifen/dm/p-ephedrine/dexbrom, guaifen/dm/pe/apap/cpm, guaifen/dm/phenylprop/pyril, guaifen/kf/sod cit(exp)/dm, guaifen/kg/dm/p-ephed/sod cit, guaifen/kg/dm/pyril/sodium cit, guaifen/kg/nacit (xp)/dm/pyril, guaifenesin/d-methorphan, guaifenesin/d-methorphan, guaifenesin/d-methorphan, guaifenesin/d-methorphan, guaifenesin/d-methorphan hb, guaifenesin/d-methorphan hb, guaifenesin/d-methorphan hbr, guaifenesin/d-methorphan hcl, guaifenesin/d-methorphan pt, guaifenesin/d-methorphan/bpm, guaifenesin/d-methorphan/pe, guaifenesin/d-methorphan/pe, guaifenesin/dm/phenylprop/bpm, guaifenesin/dm/ppa/p-tlox/cpm

GUIFEN COMBO

guafenesin/phenylephrine, guaifen/car-b-pentane/cod/cpm, guaifen/car-b-pentane/pe, guaifen/car-b-pentane/pe, guaifen/dyphyllin/ephed/pb, guaifen/dyphyllin/p-ephedrine, guaifen/pe/phenylprop/bpm, guaifen/pe/phenylprop/cod/bpm, guaifen/pe/phenylprop/cod/cpm, guaifen/pe/ppa/d-cod/pyril/cpm, guaifen/pe/ppa/hcod/phenir, guaifen/pe/ppa/pyril/cpm, guaifen/phenyleph/phenylprop, guaifen/phenylephrine/apap, guaifen/phenylephrine/bpm, guaifen/phenylephrine/cp, guaifen/phenylephrine/cpm, guaifen/phenylephrine/pyril, guaifen/ppa/cod/apap/cpm, guaifen/ppa/cod/pyril/phenir, guaifen/ppa/hcod/pyril/phenir, guaifen/ppa/hcod/slcylamd, guaifen/ppa/pyril/phenir, guaifen/ppa/pyril/phenir, guaifen/sod cit (exp)/dm, guaifen/sod citrate/dm, guaifen/sod citrate/pe/cpm, guaifen/sod citrate/theophyll, guaifen/sodium cit/dm/p-ephed, guaifen/theophyll/epd/butabarb, guaifen/theophyll/ephed/cod, guaifen/theophyll/ephed/pb, guaifenesin/carbetapentane, guaifenesin/carbetapentane, guaifenesin/carbetapentane cit, guaifenesin/carbetapentane cit, guaifenesin/codeine, guaifenesin/codeine phosphate, guaifenesin/codeine phosphate, guaifenesin/codeine/phenir, guaifenesin/dyphylline, guaifenesin/ephed/chlorphenir, guaifenesin/ephedrine, guaifenesin/ephedrine, guaifenesin/ephedrine/apap, guaifenesin/ephedrine/codeine, guaifenesin/hydrocodone, guaifenesin/hydrocodone, guaifenesin/hydrocodone bit, guaifenesin/hydrocodone/bpm, guaifenesin/hydromorphone, guaifenesin/noscapine, guaifenesin/noscapine/pe, guaifenesin/oxtriphylline, guaifenesin/pe/phenylprop, guaifenesin/pe/phenylprop, guaifenesin/phenylephrine, guaifenesin/phenylephrine, guaifenesin/phenylephrine hcl, guaifenesin/phenylephrine hcl, guaifenesin/phenylephrine/apap, guaifenesin/phenylephrine/cod, guaifenesin/phenylephrine/hcod, guaifenesin/phenylprop, guaifenesin/phenylprop, guaifenesin/phenylprop, guaifenesin/phenylprop, guaifenesin/phenylprop/apap, guaifenesin/phenylprop/bpm, guaifenesin/phenylprop/cod, guaifenesin/pot guaiaco, guaifenesin/pot guaiaco/dm, guaifenesin/theophylline

PSE-GUAI

guaifen/p-ephed hcl/dihy-cod, guaifen/p-ephed hcl/dihy-cod, guaifen/p-ephed/dihy-cod, guaifen/p-ephedrine/carbinox, guaifen/p-ephedrine/cod/cpm, guaifen/p-ephedrine/cod/cpm, guaifen/p-ephedrine/cod/tripro, guaifen/p-ephedrine/cod/tripro, guaifen/p-ephedrine/cpm, guaifen/p-ephedrine/dexbrom, guaifen/p-ephedrine/dexchlor, guaifen/theophylline/p-ephed

GUAIFENESIN PLAIN

guaifenesin, guaifenesin

PSE-DM COMBO

dm hb/p-ephed hcl/carbinox, dm tan/p-epd tan/carbinox, dm-hb/p-ephed hcl/carbinox, pseudoephedrine/dm/gg w/apap

PSE-CHLORPHENIRAMINE

chlorphen tan&pseudoeph tan, chlorphen/pse/homeopath supp, chlorphen/pseudo/m-scop, chlorphenir mal/pseudo hcl tan, pse hcl/chlor mal/dm hbr tan, pse hcl/chlor/mal hydrocod/bit, pseudoephed pl/chlorphen polis, pseudoephedrine hcl/chlor-mal, pseudoephedrine hcl/chlor-mal, pseudoephedrine hcl/chlor-mal, pseudoephedrine/chlor-mal/scop, pseudoephedrine/chlor-mal/scop, pseudoephedrine/chlorphenir, pseudoephedrine/chlorphenir, pseudoephedrine/chlorphenir

Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA)

BPCA and PREA are twp pieces of legislation passed to provide the Agency with the ability to request and require studies of products in the pediatric population. These laws do have a provision so that the FDA can obtain pediatric studies of already marketed drugs approved under section 505 of the Federal Food, Drug and Cosmetic Act.

In order to qualify for study under BPCA, a Written Request (WR) for pediatric studies must be issued by the Food and Drug Administration. A WR is issued when the drug or biological product represents a meaningful therapeutic benefit in pediatric patients or if the product is used in a substantial number of pediatric patients for the labeled indication and the absence of pediatric labeling could pose a significant risk to pediatric patients.

The WR is issued to the Sponsor of the product, and if the Sponsor declines to perform the studies, the WR can be referred to:

- The Foundation for the National Institute of Health (FNIH) if the product is on-patent, or
- The National Institute of Health if the drug is off-patent. These studies are then supported by FNIH and/or NIH.

The Sponsor cannot obtain exclusivity for an on-patent drug if they decline the WR and it is referred to the FNIH. In order for FDA to issue a WR for an off-patent drug, BPCA specifies that NIH must first place the drug on a priority list of off-patent drugs needing studies in the pediatric population. Since 2003, the NIH has updated the priority list at least annually with input from the FDA, experts in pediatric research, and the public. Monograph products are not approved under section 505 of the Federal Food, Drug and Cosmetic Act and therefore, are not eligible to be studied under BPCA regardless of patent status.

Under PREA, a pediatric assessment is required for applications with a new active ingredient, indication, dosage form, dosing regimen, or route of administration. If the FDA wants a product studied and there is not a pending application, FDA must take the following steps before a pediatric assessment is required under the marketed drug provisions of PREA:

- Issue a written request (WR) under BPCA to the Sponsor(s) of the approved application(s). (Note: A WR cannot be issued for a monograph product for the reason stated above).
- Wait a proscribed time period (180 days) for the sponsor to accept or reject the WR
  a) if the Sponsor accepts the WR, studies will be conducted under BPCA instead of PREA.
  b) if the sponsor declines the WR or does not respond to the WR within 180 days, FDA must refer the WR to the FNIH

- Wait 60 days for the Secretary to determine if there are sufficient funds in the FNIH to publicly fund the study
  a) if the Secretary certifies that there are not sufficient funds in the FNIH to publicly fund the study, PREA's marketed drugs provision can be invoked.
  b) if the Secretary certifies that there are sufficient funds, FDA must wait 270 days to determine if a contract is awarded.
  i) if a contract is awarded,the marketed drugs provision in PREA is not invoked (studies are conducted under BPCAs contracting process).
  ii) if a contract is not awarded, after 270 days, FDA can begin the process to require studies of marketed drugs under PREA.

Once the steps above are followed, PREA's marketed drugs provision can be invoked. FDA must provide notice to the Sponsor (in the form of a letter) that it is seeking to require pediatric studies and offer an opportunity for a written response and a meeting (which may include an advisory committee meeting). After any written responses are considered and any requested meetings are held, the Secretary may require the holder of the approved application to submit pediatric assessments for the approved indications in appropriate pediatric age groups under the marketed drugs provisions of PREA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

MAR 2 8 2007

Joshua M. Sharfstein, M.D.
Commissioner of Health
Baltimore City Health Department
210 Guilford Avenue, 3rd Floor
Baltimore, Maryland 21202

RE: Docket No. 2007P-0074
Comment No. CP1

Dear Dr. Sharfstein and other Petitioners,

This letter pertains to your citizen petition, submitted to FDA on March 1, 2007, filed under Docket No. 2007P-0074 in the Division of Dockets Management. The petition requests FDA to take several actions related to over-the-counter (OTC) cough and cold drug products for children under 6 years of age. In order to consider and address the issues raised in your petition, we would like clarification and additional information on the following matters:

1. The safety discussion in the petition focuses on cases of misuse, unintentional overdose, and excessive dosing of OTC cough and cold drug products. Your petition does not address the safety of OTC cough and cold drug products for children under the age of 6 when used in accordance with the labeled instructions. Please provide any data or information of which you are aware concerning the safety of these ingredients if these ingredients are used as directed on the label.

2. The petition cites several references that describe clinical efficacy studies in children. The petition concludes that these studies demonstrate that the drug products are not effective for the treatment of cough or cold symptoms. As noted in some of the Federal Register notices cited in your petition, conducting successful clinical efficacy studies in children with symptoms of cold or allergic rhinitis has always been difficult because of the limited ability of children to subjectively quantify the severity of their symptoms. Because of this, FDA has extrapolated efficacy data from adults to children, not only in the OTC monograph for cold and cough drug products, but also for the approval of pediatric indications for NDA products when the studies conducted in children failed to establish a significant effect of active therapy over placebo. Do you have comments on the use of extrapolation of efficacy data from adults to children?

   The petition emphasizes the lack of efficacy of cold and cough products in children under the age of 6. Given that the extrapolation of efficacy from adults to children has been used to determine efficacy for all children ages 2 through 12, please clarify

why you have limited your comments to children less than 6 years.

3. The petition proposes that the labeling of cough and cold products include the following statement: "These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold. These products should not be used for treatment of cough and cold in children under 6 years of age."

   Please clarify what impact you expect such labeling to have on physicians' ability or decision to prescribe cough and cold medications for children under 6 years of age.

4. The petition lists reference 23, cited to support the statement that "[i]n 2004, approximately 900 children under the age of 5 overdosed on OTC cough and cold medications in Maryland[,]" as a correspondence from the Maryland Poison Control Center. Please submit a copy of the correspondence, and provide more details on the content of this correspondence, specifically:
   a. Did the cases include cases of accidental overdose?
   b. Was there any analysis conducted that identified the root cause of these cases?
   c. Was there any data provided that describes the outcome of these cases?
   d. Did any of these cases occur with therapeutic doses?

5. The petition lists reference 24, cited to support the statement that "...over the last five years in Baltimore City, the medical examiner has linked at least four deaths of children under 4 years old to unintentional overdoses of OTC cough and cold combination drug products[,]" as a correspondence from the Maryland Office of the Chief Medical Examiner. Please provide a copy of this correspondence, and provide a description of the history of the four cases of death in children less than 4 years of age related to unintentional overdose, including any information that assisted in the determination that the deaths were linked to the use of the cough and cold products.

Please submit your response to this letter to the FDA Division of Dockets Management directed to Docket No. 2007P-0074. If you have any questions concerning this letter, you may contact Walt Ellenberg, Ph.D., at 301-796-2060.

The issues raised in this petition may be the subject of a future public discussion. If FDA proceeds with a public discussion, appropriate public notice and opportunity to participate will be provided.

Sincerely,

Charles Ganley, M.D.
Director
Office of Nonprescription Products
Center for Drug Evaluation and Research

May 2, 2007

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

RE: Docket No. 2007P-0074

Dear Dr. Ganley,

This letter responds to your request for additional information related to our recent citizen petition on over-the-counter cough and cold preparations.

1. *The safety discussion in the petition focuses on cases of misuse, unintentional overdose, and excessive dosing of OTC cough and cold drug products. Your petition does not address the safety of OTC cough and cold drug products for children under the age of 6 when used in accordance with the labeled instructions. Please provide any data or information of which you are aware concerning the safety of these ingredients if these ingredients are used as directed on the label.*

The absence of any dosing information on the label for children under the age of 2 constitutes a safety hazard for children in an age range highly vulnerable to overdose. Labeled instructions for this group of children direct parents to consult their doctor for appropriate dosing information, creating an expectation that physicians have access to evidence-based dosing information. But no such evidence exists. The result is that any dose recommended by a physician is essentially a labeled use, without any data on safety or effectiveness to support this use.

The petition references two studies reporting adverse reactions in young children ingesting recommended doses of cough and cold preparations.[1,2] Of larger concern, however, is the lack of evidence demonstrating safety at recommended doses. A defining feature of over-the-counter products is a wide therapeutic window. Yet there is insufficient evidence currently available to establish a wide margin of safety in cough and cold preparations.

The petition's main point on safety is the danger of misuse of these products. Multiple studies, including a recent paper in Morbidity and Mortality Weekly reports by

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[1] Sills JA, Nunn AJ, Sankey RJ. Visual hallucinations in children receiving decongestants. *British Medical Journal* 1984;**288**(6434):1912-1913.

[2] Joseph MM, King WD. Dystonic reaction following recommended use of a cold syrup. *Annals of Emergency Medicine* 1995;**26**(6):749-51.

the Centers for Disease Control and Prevention, have linked the death of children to over-the-counter cough and cold preparations.

There is ample historical precedent for FDA intervention in the interest of protecting consumers from risks associated with misuse of a product. FDA's intervention has ranged from changes to warnings and labeling to removing products from the market.

In 2006, for example, FDA published a Proposed Amendment to a Tentative Final Monograph on internal analgesic products. This Proposed Amendment was developed in response to numerous cases linking unintentional acetaminophen overdose to severe hepatotoxicity. In this case, the FDA determined that public health could be protected by strengthening the warnings and labeling requirements on these products. (71 FR 77316)

Where, as in this case, there is little or no benefit to the products, FDA has taken stronger regulatory action to protect harm from product misuse. In 1982, FDA issued a rule declaring camphorated oil products to be not generally recognized as safe for human use. This ruling, which was justified by "the potential for accidental ingestion and toxicity" (47 FR 41716), followed an FDA investigation into a series of accidental camphor poisonings among children and adults who had confused the medication with another product.

While FDA considered several alternative regulatory routes to reducing the risk of unintentional camphorated oil ingestion, the agency concluded that "the risk [of accidental poisonings] is unacceptable in light of the marginal therapeutic value of the product." (47 FR 41717)

2. *The petition cites several references that describe clinical efficacy studies in children. The petition concludes that these studies demonstrate that the drug products are not effective for the treatment of cough or cold symptoms. As noted in some of the Federal Register notices cited in your petition, conducting successful clinical efficacy studies in children with symptoms of cold or allergic rhinitis has always been difficult because of the limited ability of children to subjectively quantify the severity of their symptoms. Because of this, FDA has extrapolated efficacy data from adults to children, not only in the OTC monograph for cold and cough drug products, but also for the approval of pediatric indications for NDA products when the studies conducted in children failed to establish a significant effect of active therapy over placebo. Do you have comments on the use of extrapolation of efficacy data from adults to children?*

Extrapolation of efficacy data from adults to children is inappropriate for cough and cold preparations for the following four reasons:

(a) Valid data is available without requiring extrapolation.

When valid studies of drug efficacy in children have failed to show benefit, the evidence would suggest that these drugs should not be used in children. While pediatric

research is limited by the ability of children to judge and communicate their symptom severity, there are alternative approaches to obtaining valid data.

Multiple randomized, placebo-controlled trials on over-the-counter cough and cold preprations have successfully used parent questionnaires as a surrogate measure for symptom severity.[3,4] These studies have found negative results, suggesting that extrapolation is not necessary for this drug class.

(b) Differences in underlying physiology and mechanisms of disease make the pathogenesis of respiratory illness in children and adults dissimilar.

The Institute of Medicine has advised that the "extrapolation to children of safety and efficacy data generated for adults requires careful attention to potentially important differences between these two populations."[5]

Respiratory anatomy distinguishes adult and pediatric populations; incomplete development of paranasal sinuses and reduced diameter of airways significantly influence the frequency and severity of respiratory illness in children.

Physiology also plays a significant role in both the development of disease and the response to medications. Maturational differences in respiratory muscle and chest wall structure may influence the signs and duration of illness. In addition, immaturity of hepatic enzyme systems can have considerable impact on drug metabolism and clearance of medicines.[6]

Evidence from animal studies also suggests that the physiology of drug action for some cough and cold drug classes may differ between adults and children. Studies on catecholamine drug action in the lamb, for example, have demonstrated that blood pressure and cardiac contractility responses may be associated with age-related differences in both receptor numbers and receptor response.[7]

---

[3] Schroeder K, Fahey T. Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials. *Archives of Disease in Childhood* 2002;**86**:170-175.

[4] Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *The Cochrane Database of Systematic Reviews* 2004;(4):CD001831.

[5] Yaffe S (Ed). 2000. *Rational Therapeutics for Infants and Children; Workshop Summary*. The National Academies Press.

[6] Kearns GL, Reed MD. Clinical pharmacokinetics in infants and children. A reappraisal. *Clinical Pharmacokinetics* 1989;**17**(suppl 1): 29-67.

[7] Teitel DF, Sidi D, Chin T et al. Developmental changes in myocardial contractile reserve in the lamb. *Pediatric Research* 1985;**19**:948–955.

The American College of Chest Physicians notes that "the pattern of respiratory illness in children is clearly different from that in adults; for example, viruses associated with the common cold in adults can cause serious respiratory illnesses such as bronchiolitis and croup in previously well children."[8]

(c) Diagnostic considerations undermine the validity of extrapolation.

The differential diagnosis for nonspecific indicators of disease like cough, nasal congestion and difficulty breathing varies widely between adults and children. In one recent study on children with chronic cough, the authors reported that common causes of adult cough were found in less than 10% of children.[9] Many children who with cough may have alternative, serious diagnoses, including asthma and pneumonia.

These diagnostic differences complicate the extrapolation of efficacy data from adults to children. Even if we were to assume that (1) a product reduces the symptoms of the common cold in adults and (2) the physiology of adults and children makes extrapolation appropriate for efficacy for the common cold, then one would still have to prove (3) parents would use the drug for the right condition. Otherwise, administration of drugs for inappropriate conditions confers a risk of adverse effects with no potential benefit, and additionally may delay medical treatment or diagnosis of more serious disorders.

(d) Extrapolation is an inappropriate basis for aggressive marketing.

Commercial marketing campaigns promoting particular products for children should be based upon pediatric data. Otherwise, as is the case for over-the-counter cough and cold preparations, consumers can be misled about the scientific basis for the products' use.

3. *The petition emphasizes the lack of efficacy of cold and cough products in children under the age of 6. Given that the extrapolation of efficacy from adults to children has been used to determine efficacy for all children ages 2 through 12, please clarify why you have limited your comments to children less than 6 years.*

We chose to focus on children under the age of 6 because of the high frequency of inappropriate dosing and accidental ingestion in this age group, and the fact that smaller body size makes them particularly vulnerable to overdose. We would not object to an FDA inquiry that includes children under 12. However, based on our review of the data, we would urge FDA to act on the under 6 population now.

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[8] Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**(1 Suppl):260S-283S.

[9] Marchant JM, Masters IB, Taylor SM, *et al.* Evaluation and outcome of young children with chronic cough. *Chest* 2006;**129**:1132–41.

Please clarify what impact you expect such labeling to have on physicians' ability or decision to prescribe cough and cold medications for children under 6 years of age.

Revised labeling would not affect the legal ability of physicians to prescribe cough and cold preparations for use in children under 6 years of age.

Together with the FDA public statement requested by the petition, however, labeling changes would alert physicians that the adminstration of over-the-counter cough and cold preparations to young children is not supported by evidence. It would also reduce the current expectation of both parents and physicians that healthcare providers should have access to evidence-based dosing information. This expectation is driven by the labeling instructing parents to consult their doctors on the appropriate dose.

We anticipate that these factors would reduce the overall use of these medications, both with and without prescriptions.

4. *The petition lists reference 23, cited to support the statement that "[i]n 2004, approximately 900 children under the age of 5 overdosed on OTC cough and cold medications in Maryland[,]" as a correspondence from the Maryland Poison Control Center. Please submit a copy of the correspondence, and provide more details on the content of this correspondence...*

Calls to the Maryland Poison Center are reported in an annual publication. The 2004 publication can be found online at http://www.mdpoison.com/publications/county_pdf_2004/maryland_total_2004.pdf, with specific references to cough and cold medications in children under 5 years of age on page 26.

The Maryland Poison Center was unable to provide further details regarding the dosages involved and the outcome of these cases.

5. *The petition lists reference 24, cited to support the statement that "...over the last five years in Baltimore City, the medical examiner has linked at least four deaths of children under 4 years old to unintentional overdoses of OTC cough and cold combination drug products[,]" as a correspondence from the Maryland Office of the Chief Medical Examiner. Please provide a copy of this correspondence, and provide a description of the history of the four cases of death in children less than 4 years of age related to unintentional overdose, including any information that assisted in the determination that the deaths were linked to the use of the cough and cold products.*

We would recommend that FDA contact the Maryland Office of the Medical Examiner. The case files for the children involved are available through that office, and the cases are summarized briefly below:

- 3 year old African American male
  Cause of death: Doxylamine intoxication

Circumstances: Child found unresponsive after receiving multiple doses of cold medications to treat gastroenteritis and fever.

- 17 month old African American male
  Cause of death: Multidrug intoxication complicating influenza, pneumonitis and acute bronchitis
  Circumstances: Child was given multiple doses of adult formulation cold medication for respiratory symptoms

- 3 month old male
  Cause of death: Multidrug intoxication complicating sudden unexplained death in infancy (SUDI)
  Circumstances: Child received two doses of adult formulation cold medication 5 hours apart

- 9 month old male
  Cause of death: Mixed drug intoxication
  Circumstances: Child experienced cardiopulmonary arrest after being given over-the-counter cold medication for cough, fever and irritability

The agency should be aware of a new study reporting the deaths of 13 infants and toddlers under the age of 16 months in which over-the-counter cough and cold medications were the direct cause of death or a contributing factor.[10] This study analyzed records of infant and toddler deaths in the Philadelphia region between 1999 and 2005, and found that "the administration of OTC cold medication to infants continues to present a serious health hazard."

There are now at least 25 deaths of young children associated with over-the-counter cough and cold preparations in the medical literature and known to us.[10,11,12,13,14]

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[10] Wingert WE, Mundy LA, Collins GL, Chmara ES. Possible Role of Pseudoephedrine and Other Over-the-Counter Cold Medications in the Deaths of Very Young Children. *Journal of Forensic Science* 2007;**52**(2):487-490.

[11] Gunn VL, Taha SH, Liebelt EL, Serwint JR. Toxicity of over-the-counter cough and cold mediations. *Pediatrics* 2001;**108**(3):e52.

[12] Litovitz T, Manoguerra A. Comparison of Pediatric Poisoning Hazards: An Analysis of 3.8 Million Exposure Incidents. A Report from the American Association of Poison Control Centers. *Pediatrics* 1992;**89**(6 Pt 1): 999-1006.

[13] Centers for Disease Control and Prevention. Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005. *MMWR* 2007 Jan 12;**56**(01):1-4.

[14] Sharfstein JM et al. The Baltimore Statement on the Use of Over-the-Counter Cough and Cold Medications by Children Five and Under. Available at http://www.ci.baltimore.md.us/government/health/press/OTCstatement.pdf.

We urge the agency to act quickly.

Sincerely,

Joshua M. Sharfstein, M.D.
Commissioner of Health
Baltimore City Health Department

Marisa L. North
Johns Hopkins School of Medicine
Class of 2008

Laura Herrera, M.D., MPH
Chief Medical Officer
Baltimore City Health Department

Michael Burke, M.D.
Chairman of Pediatrics
St. Agnes Hospital

Wayne R. Snodgrass, M.D., Ph.D.
Professor, Pediatrics and Pharamcology-Toxicology
Head, Clinical Pharamcology-Toxicology Unit
Medical Director, Texas Poison Center – Houston/Galveston
University of Texas Medical Branch

Janet Serwint, M.D.
Professor of Pediatrics
Johns Hopkins Hospital

Kima Joy Taylor M.D., MPH
Deputy Commissioner
Baltimore City Health Department

Anne Bailowitz, M.D., MPH
Chief, Bureau of Child Health and Immunization
Baltimore City Health Department

Michael Shannon, M.D., MPH
Chief and CHB Chair
Division of Emergency Medicine
Children's Hospital Boston
Professor of Pediatrics
Harvard Medical School

Victoria Tutag Lehr, Pharm.D
Associate Professor
Department of Pharmacy Practice
The Eugene Applebaum College of Pharmacy & Health Sciences
Division of Clinical Pharmacology,
Children's Hospital of Michigan
Wayne State University

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUL 18 2007

Joshua M. Sharfstein, M.D.
Commissioner of Health
Baltimore City Health Department
210 Guilford Avenue, 3rd Floor
Baltimore, Maryland 21202

RE: Docket No. 2007P-0074
Comment No. CP1, SUP1, LET1, LET2
LET3 & LET4

Dear Dr. Sharfstein,

This letter pertains to your citizen petition, submitted to FDA on March 1, 2007, filed under Docket No. 2007P-0074 in the Division of Dockets Management. The petition requests FDA to take several actions related to over-the-counter (OTC) cough and cold drug products for children under 6 years of age. In addition, we also refer you to our letter dated, March 28, 2007 which requested clarification on various items identified in your petition (see Attachment 1).

Specifically, in a March 28, 2007, letter, we requested the following clarification on information cited in your citizen petition:

> "The petition lists reference 24, cited to support the statement that "...over the last five years in Baltimore City, the medical examiner has linked at least four deaths of children under 4 years old to unintentional overdoses of OTC cough and cold combination drug products[,]" as a correspondence from the Maryland Office of the Chief Medical Examiner. Please provide a copy of this correspondence, and provide a description of the history of the four cases of death in children less than 4 years of age related to unintentional overdose, including any information that assisted in the determination that the deaths were linked to the use of the cough and cold products."

In your response to the FDA, dated May 2, 2007 (see Attachment 2), you recommended that FDA contact the Maryland Office of the Medical Examiner to obtain the case files for the children involved. On May 3 and 23, 2007, FDA contacted the Chief Medical Examiner for the State of Maryland via telephone to obtain details of the cases described in your petition (see Attachment 3). On June 7, 2007, FDA sent a letter to the Chief Medical Examiner for the State of Maryland outlining the request for the information detailed above that you cited in your citizen petition (see Attachment 4).

The Chief Medical Examiner for the State of Maryland responded on June 11, 2007, via email, and indicated that he has no record of correspondence between his office and the Baltimore City Health Department and further described his efforts to obtain this information from your office (see Attachment 5).

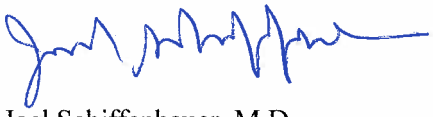
To date, the FDA has not been able to obtain the information referenced in your petition regarding four deaths of children under 4 years old to unintentional overdoses of OTC cough and cold combination drug

in Baltimore city. Therefore, we are again requesting that you provide the case reports which you referenced in your citizen petition or contact the medical examiner to identify for them the case files referenced in the petition. We would like to emphasize that you are responsible for providing all referenced information pertaining to a citizen petition according to 21 CFR 10.30(b) and 21 CFR 10.20(c)(4) (see Attachment 6).

Please submit your response to this letter to the FDA Division of Dockets Management directed to Docket No. 2007P-0074. If you have any questions concerning this letter, you may contact Walt Ellenberg, Ph.D., at 301-796-2060.

The issues raised in this petition may be the subject of a future public discussion. If FDA proceeds with a public discussion, appropriate public notice and opportunity to participate will be provided.

Sincerely,



Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Ellenberg, Walter

From: Sharfstein, Josh M.D. [redacted]
Sent: Friday, July 20, 2007 6:59 PM
To: Sharfstein, Josh M.D.; Schiffenbauer, Joel
Cc: Ellenberg, Walter; [redacted]
Subject: pediatric deaths associated with OTC cough-and-cold medication
Importance: High
Attachments: informal case notes.doc; pediatrics.pdf; emails.tiff; 3 death certificates.tiff

Dear Dr. Schiffenbauer and Dr. Ellenberg,

This email is in reply to your letter of July 18 regarding the 4 deaths of children under 4 years old. I spoke today with Dr. David Fowler, Chief Medical Examiner for the State of Maryland.

As Dr. Fowler noted, the Health Department originally became aware of these deaths through the Child Fatality Review Committee. This is an interagency committee that examines all unexplained child deaths in Baltimore City. At the committee meetings, an assistant medical examiner provides the causes of death and toxicology results.

We subsequently went back and confirmed the cases with the Office of the Chief Medical Examiner.

Please find four files attached--

1. An informal summary of the four cases -- these are our internal Health Department notes. The cases are (1) a 3-year old who died in 2001, (2) a 17-month old who died in 2003, (3) a 3-month old who died in 2006, and (4) a 9-month old who died in 1999.

2. Death reports for three of the four cases. Note that this computer file includes five death reports. Two of the children had two death reports filed each -- one while the causes of death was blank, and the other after toxicology results became available. The Health Department does not have the death report on hand for the fourth case, because we do not keep these records from 1999.

3. A copy of a 2001 publication in *Pediatrics*. Case 3 in this paper summarizes case (4) -- the one from 1999.

4. Email correspondence between the Health Department and an assistant medical examiner from November and December 2006 documenting that the Medical Examiner has the four case files.

If the attached documents do not meet your needs, please do not hesitate to email or call me [redacted]<<informal case notes.doc>> <<pediatrics.pdf>> <<emails.tiff>> <<3 death certificates.tiff>> . Dr. Fowler indicated he would be happy to meet with the FDA team to discuss these four deaths. He is cc'd on this message, and his phone number is [redacted]

[redacted].

Have a great weekend.

Sincerely,

Josh

Joshua M. Sharfstein, M.D.
Commissioner of Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN - 7 2007

David Fowler, M.D.
Chief Medical Examiner, State of Maryland
111 Penn St.
Baltimore, MD 21201

Dear Dr. Fowler,

This letter pertains to a citizen petition, submitted to FDA on March 1, 2007, which requests that FDA take several actions related to the over-the-counter (OTC) cough and cold drug products for children under 6 years of age (see enclosed petition).

The petition lists reference 24, cited to support the statement that "...over the last five years in Baltimore City, the medical examiner has linked at least four deaths of children under 4 years old to unintentional overdoses of OTC cough and cold combination drug products" as a correspondence from the Maryland Office of the Chief Medical Examiner. Please provide a description of the history of the four cases of death in children less than 4 years of age (3 year old African American male, 17 month old African American male, 3 month old male, 9 month old male) related to unintentional overdose, including any information that assisted in the determination that the deaths were linked to the use of cough and cold products.

If possible, we would like to receive a response to this inquiry within one month so that we can incorporate the information in our deliberations You should not provide any information that is deemed confidential because this information will be made available to the public. If you have any questions about this request, please contact Dr. Joel Schiffenbauer, Division of Nonprescription Clinical Evaluation, FDA (by phone at 301-796-1288 or by e-mail at joel.schiffenbauer@fda.hhs.gov).

Sincerely,

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN - 7 2007

Douglas E. Henley, M.D.
Executive Vice President
American Academy of Family Physicians
P.O. Box 11210
Shawnee Mission, Kansas 66207-1210

Dear Dr. Henley,

This letter pertains to a citizen petition, submitted to FDA on March 1, 2007, which requests that FDA take several actions related to the over-the-counter (OTC) cough and cold drug products for children under 6 years of age (see enclosed petition). In order to consider and address the issues raised in this petition, we are interested in the position of the American Academy of Family Physicians (AAFP) on some of the issues as outlined below.

1. The petition proposes that the labeling of the cough and cold products include the following statements: "These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold. These products should not be used for treatment of cough and cold in children under 6 years of age."

   We are interested in the opinion of the AAFP on the labeling that would be appropriate for OTC cough and cold drug products for children.

   Please describe what impact, if any, you anticipate labeling changes, such as the ones proposed in the petition, would have on physicians' decision to prescribe cough and cold medications for children under 6 years of age.

2. The petition cites several references that describe clinical efficacy studies in children. The petition concludes that these studies demonstrate that the OTC cough and cold drug products are not effective for treatment of cough or cold symptoms in children. As you know, conducting successful clinical efficacy studies in children with symptoms of cold or allergic rhinitis has always been difficult due, in large part, to the limited ability of children to subjectively quantify the severity of their symptoms. Because of this, FDA has extrapolated efficacy data from adults to children, not only in the OTC monograph for cold and cough drug products, but also for the approval of pediatric indications for NDA products when the studies conducted in children failed to establish a significant effect of active therapy over placebo.

   a. Do you have comments on the use of extrapolation of efficacy data from adults to children in general and for OTC cough and cold products specifically?

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN - 7 2007

Douglas E. Henley, M.D.
Executive Vice President
American Academy of Family Physicians
P.O. Box 11210
Shawnee Mission, Kansas 66207-1210

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2. The petition cites several references that describe clinical efficacy studies in children. The petition concludes that these studies demonstrate that the OTC cough and cold drug products are not effective for treatment of cough or cold symptoms in children. As you know, conducting successful clinical efficacy studies in children with symptoms of cold or allergic rhinitis has always been difficult due, in large part, to the limited ability of children to subjectively quantify the severity of their symptoms. Because of this, FDA has extrapolated efficacy data from adults to children, not only in the OTC monograph for cold and cough drug products, but also for the approval of pediatric indications for NDA products when the studies conducted in children failed to establish a significant effect of active therapy over placebo.

   a. Do you have comments on the use of extrapolation of efficacy data from adults to children in general and for OTC cough and cold products specifically?

AAFP Comments on Labeling of Over the Counter Cold medicine for children
(Review of Citizens Petition and FDA Advisory)

- The FDA advisory offers good, common sense advice for parents.
- Children get colds frequently and cold medicines do not cure colds; they usually are not needed and only improve some of the symptoms. There is even some doubt that they do that. A review in JAMA in 1993 found that: No good evidence has demonstrated the effectiveness of over-the-counter cold medications in preschool children. Further studies are required to clarify the role of these medications in children as extrapolation of efficacy studies from adults to children cannot be made.
- Cold medicines contain ingredients that are potentially dangerous and that can interact with other medications. Serious complications are rare when the medications are used correctly.
- The FDA advisory re-emphasizes the value of a medical home for each patient, especially young children.

The FDA advisory states: (The most important items to stress are underlined.)

- Do ***not*** use cough and cold products in children under 2 years of age UNLESS given specific directions to do so by a healthcare provider.

- Do not give children medicine that is packaged and made for adults. Use only products marked for use in babies, infants or children (sometimes called "pediatric" use).

- Cough and cold medicines come in many different strengths. If you are unsure about the right product for your child, ask a healthcare provider.

- If other medicines (over-the-counter or prescription) are being given to a child, the child's healthcare provider should review and approve their combined use.

- Read all of the information in the "Drug Facts" box on the package label so that you know the ***active ingredients*** and the ***warnings***.

- Follow the ***directions*** in the "Drug Facts" box. Do not give a child medicine more often or in greater amounts than is stated on the package.

- Too much medicine may lead to serious and life-threatening side effects, particularly in children aged 2 years and younger.

- For liquid products, parents should use the measuring device (dropper, dosing cup or dosing spoon) that is packaged with each different medicine formulation and that is marked to deliver the recommended dose. A kitchen teaspoon or tablespoon is not an appropriate measuring device for giving medicines to children.

- If a measuring device is not included with the product, parents should purchase one at the pharmacy. Make sure that the dropper, dosing cup or dosing spoon has markings on it that match the dosing that is in the ***directions*** in the "Drug Facts" box on the package label, or is recommended by the child's health care provider.

- If you DO NOT UNDERSTAND the instructions on the product, or how to use the dosing device (dropper, dosing cup or dosing spoon), DO NOT USE the medicine. Consult your healthcare provider if you have questions or are confused.

- Cough and cold medicines only treat the symptoms of the common cold such as runny nose, congestion, fever, aches, and irritability. They do not cure the common cold. Children get better with time.

- If a child's condition worsens or does not improve, stop using the product and immediately take the child to a health care provider for evaluation.

http://www.fda.gov/cder/drug/advisory/cough_cold.htm

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN - 7 2007

Bruce Anderson, Pharm.D.
Director
Maryland Poison Center
University of Maryland at Baltimore
School of Pharmacy
20 North Pine Street, PH 772
Baltimore, MD 21201

Dear Dr. Anderson,

This letter pertains to a citizen petition, submitted to FDA on March 1, 2007, which requests that FDA take several actions related to the over-the-counter (OTC) cough and cold drug products for children under 6 years of age (see enclosed petition). In order to consider and address the issues raised in this petition, we are interested in obtaining details of the cases reported in your 2004 Poison Control Center Activity Report.

a. Specifically, the petition lists reference 23, cited to support the statement that "[i]n 2004, approximately 900 children under the age of 5 overdosed on OTC cough and cold medications in Maryland" as a correspondence from the Maryland Poison Control Center. We would like to obtain information in regards to cases for cold and cough products in general and specifically for those cases that required admission to a critical care unit or admission to a non-critical care unit. The report provides the breakdown for outcomes for all cases in children less than 5 years of age but does not break it down by drug category. For these cases we would like to obtain the following information if available:

a. Please provide a brief description of the case.
b. Was there any analysis conducted that identified the root cause of these cases?
c. Did any of these cases occur with therapeutic doses?
d. Did the cases include cases of accidental overdose?
e. Was there any data provided that describes the outcome of these cases?

If possible, we would like to receive a response to this inquiry within two months so that we can incorporate this information in our deliberations. You should not provide any information that is deemed confidential because this information will be made available to the public. If you have any questions about this request, please contact Dr. Joel Schiffenbauer, Division of Nonprescription

Clinical Evaluation, FDA (by phone at 301-796-1288 or by e-mail at joel.schiffenbauer@fda.hhs.gov).

Sincerely,

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Maryland Poison Center
University of Maryland School of Pharmacy

July 31, 2007

Joel Schiffenbauer, M. D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD 20857

Dear Dr. Schiffenbauer;

I am writing in response to your request for additional information on cough and cold exposures to children less than 6 years of age reported to the Maryland Poison Center in 2004. Enclosed is a report outlining summary information about those calls; specifically, calls to the Maryland Poison Center where only one substance was involved in the exposure in children < 6 years old and with the substance coded as being a cough and cold product. The report provides summary information on these calls by generic product category and by reason for exposure.

You will note that the total call volume is slightly different than what was included in the Maryland Poison Center Annual Report from 2004. This report was an ad-hoc report that was specifically designed to report exposures to agents categorized as cough and cold products. The 2004 annual report data was from a different report that may have excluded some of the products that were included in this report.

As you can tell from this report, the vast majority of cases resulted in either no effect or only minor symptoms. Most calls in this age group were categorized as "unintentional general", meaning, kids getting into products found in their home. This is not unexpected. In our experience, toddlers exploring their environment encounter substances that are commonly available. These products are commonly available in many homes.

Only five cases out of 1,078 that were reported to the Maryland Poison Center were coded as having symptoms consistent with an outcome of "moderate effect". One occurred in a product containing only diphenhydramine, one involved an exposure to a nasal decongestant (excluding tetrahydrazoline), one involved a product formulated for adults that contained acetaminophen, and one involved an exposure to a product that contained an antihistamine, a

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Certified as a Regional Poison Center by the American Association of Poison Control Centers

decongestant, and some type of opioid, and the last was an exposure to a combination product with antihistamine plus a decongestant. Four of these five cases were coded as being unintentional-general exposures. One was coded as an adverse reaction (4 month old child developed tachycardia after being dosed with a decongestant). All of the children in these cases had complete resolution of symptoms with appropriate supportive care.

If you have any questions, I'd be happy to try to answer them.

Sincerely,

Bruce D. Anderson, PharmD, DABAT
Director
Associate Professor

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN - 7 2007

Errol Alden, M.D.
Executive Director
American Academy of Pediatricians
141 Northwest Point Blvd.
Elk Grove Village, Illinois 60007

Dear Dr. Alden,

This letter pertains to a citizen petition, submitted to FDA on March 1, 2007, which requests that FDA take several actions related to the over-the-counter (OTC) cough and cold drug products for children under 6 years of age (see enclosed petition). In order to consider and address the issues raised in this petition, we are interested in the position of the American Academy of Pediatrics (AAP) on some of the issues as outlined below.

1. The petition proposes that the labeling of the cough and cold products include the following statements: "These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold. These products should not be used for treatment of cough and cold in children under 6 years of age."

   We are interested in the opinion of the AAP on the labeling that would be appropriate for OTC cough and cold drug products for children.

   Please describe what impact, if any, you anticipate labeling changes, such as the ones proposed in the petition, would have on physicians' decision to prescribe cough and cold medications for children under 6 years of age.

2. The petition cites several references that describe clinical efficacy studies in children. The petition concludes that these studies demonstrate that the OTC cough and cold drug products are not effective for treatment of cough or cold symptoms in children. As you know, conducting successful clinical efficacy studies in children with symptoms of cold or allergic rhinitis has always been difficult due, in large part, to the limited ability of children to subjectively quantify the severity of their symptoms. Because of this, FDA has extrapolated efficacy data from adults to children, not only in the OTC monograph for cold and cough drug products, but also for the approval of pediatric indications for NDA products when the studies conducted in children failed to establish a significant effect of active therapy over placebo.
   a. Do you have comments on the use of extrapolation of efficacy data from adults to children in general and for OTC cough and cold products specifically?

If possible, we would like to receive a response to this inquiry within three months so that we can incorporate the position of the Academy in our deliberations If you have any questions about this request, please contact Dr. Joel Schiffenbauer, Division of Nonprescription Clinical Evaluation, FDA (by phone at 301-796-1288 or by e-mail at joel.schiffenbauer@fda.hhs.gov)

The issues raised in this petition may be the subject of a future public discussion. If FDA proceeds with a public discussion, appropriate public notice and opportunity to participate will be provided.

Sincerely,

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

September 6, 2007

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Elk Grove Village, IL 60007-1098
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Joel Schiffenbauer, MD
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire
Silver Spring, MD 20993

Dear Dr Schiffenbauer:

Thank you for your June 2007 letter seeking the opinion of the American Academy of Pediatrics (AAP) concerning the use of over-the-counter (OTC) cough and cold products in children under six years of age. As an organization of 60,000 pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults, the AAP has been an outspoken advocate for the study of pharmaceuticals in the pediatric population through well-designed clinical trials and for pediatric safety and efficacy information to be disseminated as widely as possible. Although the March 2007 Citizen's Petition raises a number of very important issues pertaining to the approval, labeling, and promotion of over-the-counter cough and cold products intended for children, the following comments are directed toward the questions posed in your letter.

1.a. *We are interested in the opinion of the AAP on the labeling that would be appropriate for OTC cough and cold drug products for children.*

Appropriate labeling should reflect the evidence-based benefits of the use of these products in children, the risks associated with their use, and accurate dosing information so that children's health care providers can make an informed decision as to whether or not to recommend use of these products and counsel parents appropriately should they choose to do so.

1. As for the efficacy of these compounds, the published literature on the benefits of these preparations does not support their use in children at this age.[1-9] Not only have these products "not been found to be safe or effective in children under six years of age for the treatment of cough and cold," as is stated in the petition, but also, they have (with the exception of pseudoephedrine, for which there are no pediatric data) been found not to be effective in this population at all.[1-9] This distinction is an important one. This is not a situation in which pediatric data are lacking and we are unable to say one way or the other whether or not these products work in children. Multiple peer-reviewed studies have concluded these medications and combinations are not effective at the currently recommended doses in children.[1-9] The AAP, American College of Chest Physicians, and Cochrane Collaboration have reached this same conclusion.[6,10,11]

   As for the risks, these products are generally well tolerated in children when given in accord with labeling. However, there are at least two important situations in which children are placed at greater risk of the serious adverse events described in the petition.

The first of these relates to the frequent misdosing of these preparations. The OTC cough and cold medications and antihistamines were the sixth and tenth most frequent exposures in children under six years of age reported to US poison control centers in 2005, accounting for more than 100,000 cases.[12] The 1998 pediatric data from the American Association of Poison Control Centers (the most recent published set to break out pediatric data on children under six years of age) demonstrate that 15% of the children received an inappropriate dose of these medications and required treatment.[13] Contributing to this problem is the availability of multi-ingredient preparations that could lead to inaccurate dosing as a result of a caregiver misunderstanding the active ingredients when administering more than one preparation. For example, a "cough and allergy" preparation may contain the same ingredient as one labeled as "chest and nasal congestion." This is made even more complex by the variability in titles given by different manufacturers.

The second source of risk is the complete lack of data to support a therapeutic rationale for dosing in the pediatric population. When parents are advised to "consult with a physician" for the appropriate dose of these preparations in their infant or young child, they expect that the physician has access to evidence-based information on which to base a decision, but this information is nonexistent. Furthermore, the need to consult with a physician is inconsistent with the classification of these medications as OTC. The prescription exemption procedure classifies OTC medications as those that are "safe and effective for use in self-medication as directed in proposed labeling."[14] Requiring parents to consult their physician for a dose in their infant or child represents an unacceptable shift of responsibility for proper dosing from the manufacturer to the physician, who, given the current absence of data to show that these medications even work, has no rational basis for their dosing.

The potential for inaccurate dosing is further exacerbated by the apparent greater sensitivity of children under the age of two years to the potentially fatal effects of some of the more common ingredients in these preparations.[15-17] Further, although most medications taken by children are currently dosed in a mg/kg fashion, data describing this dosing scheme for most of these medications are unavailable. A notable exception is diphenhydramine.

The OTC cough and cold products, therefore, constitute a group of drugs that do not produce any discernable health benefits in this population according to the published peer-reviewed literature. As such, any associated risks from these treatments, irrespective of how infrequent or small, are unacceptable given the lack of benefit obtained. This demonstrated lack of efficacy, combined with the frequent misuse, lack of rational basis for dosing, and apparent increased sensitivity to toxicity of these preparations in children under six years of age, are of considerable concern.

The AAP, therefore, suggests the following changes to the labeling of these products:

1. Clear, evidence-based pediatric dosing guidelines should be provided for all ages, especially for the vulnerable population under the age of two years. If no such dosing data are available for a specific age group, as is the case currently, then these preparations do not meet criteria for and should not be available for OTC use in that age group.

2. The following statement should be provided as the default labeling of these preparations until adequate data have been produced: "*This product has been shown to be ineffective in the treatment of cough and cold in children under the age of six years. Serious adverse reactions, including but not limited to death, have been reported with its use, misuse, and abuse*." As pediatric data are generated, the wording can be modified to reflect increasing understanding of the efficacy and safety of these medications.

1.b. *Please describe what impact, if any, you anticipate labeling changes, such as the ones proposed in the petition, would have on physicians' decision to prescribe cough and cold medications for children less than 6 years of age.*

Physicians, pharmacists, and parents alike are motivated by a well-intentioned desire to help a child who is uncomfortable during an upper respiratory infection by providing some symptomatic relief. However, many clinicians may not be aware of how ineffective these treatments are or the dangers associated with their use and misuse. The result is that many pediatricians will recommend these products, even for infants.[18]

Because of the unlimited availability, current labeling, and extensive marketing of OTC cough and cold products, parents have an expectation that these products are an effective and safe treatment option to help their sick child. By bringing this information to the fore through the new labeling, parents will have a better understanding of the lack of efficacy and potential risks of these preparations. Pharmacists and physicians will benefit from the labeling changes in two ways. The first is that they, too, will be made aware of the limitations and dangers of these products, and with this knowledge they will be less likely to recommend these to the parents of their patients. The second benefit will be in a potential change in parental expectations. This may result in a decreased pressure to offer something to a parent with an ill child (the therapeutic imperative).

To have the greatest effect, the labeling changes will need to inform and affect multiple levels: physicians, pharmacists, and parents. Exclusion of any group will create confusion and inconstancy, decreasing the benefits of the proposed labeling changes.

1.c. *Do you have comments on the use of extrapolation of efficacy data from adults to children in general and for OTC cough and cold products specifically?*

Extrapolation of therapeutic data from adults to children, although common, is fraught with danger. As has often been stated, children are not small adults. Reliance on adult studies presumes that study design and statistical analyses are linear across adult and pediatric populations, which is not the case. Age-related developmental variability in the four components of pharmacokinetics (absorption, distribution, metabolism, and elimination) and in pharmacodynamics has been described. Although they are, as yet, incompletely understood, there are clear data to show that adults and children handle and respond to drugs differently.

Drug absorption in children is affected by variability in gastric pH, bowel surface area, transit time, and the expression of transporters. Distribution of drugs changes considerably throughout childhood as a

function of changes in physiological volumes, drug binding in various compartments, and the types and numbers of transporters. Metabolism is likely the greatest source of pharmacokinetic variability between children and adults and is influenced by changes in hepatic blood flow, drug extraction, and age-related expression of metabolic enzymes. Developmental changes in elimination are largely a function of renal maturation, with glomerular filtration rate and tubular secretion being decreased at birth through early infancy. Pharmacodynamics change considerably throughout childhood as receptor number and function, other signal transduction mechanisms, and the responsive capability of the organs develop.

Even if extrapolation of adult data to children were scientifically appropriate, it is unnecessary in the case of most OTC cough and cold products, which have been studied in children and found to be ineffective.[1-9] Cough suppressants have been studied in children and have been shown not to offer any benefits over placebo.[3,6,9,14] Antihistamines have had a similar lack of efficacy in children (and in adults), when used alone or in combination with decongestants, for the treatment of cold symptoms.[3,4,6,7] The evidence in adults to support the use of decongestants is minimal and supportive of only one drug, pseudoephedrine.[8] Pseudoephedrine has been shown in adults to offer a small (approximately 6%) decrease in symptoms versus placebo, but there are insufficient data to support its use in children and no reports of positive benefits associated with its use.[8] Many OTC products have substituted pseudoephedrine with phenylephrine, which has been shown to be of no benefit as a decongestant in children (or adults).[2,8,19,20]

From first principles, then, extrapolation of adult data to children is imprecise and should be avoided whenever possible. Fortunately, this is not required in the majority of OTC cough and cold remedies, because the available pediatric data fail to show any benefit to their use.

The AAP applauds the decision of the Food and Drug Administration to review the safety and efficacy of cough and cold products intended for children and looks forward to future opportunities to assist the FDA in promoting rational therapeutics for children.

Sincerely,

Jay E Berkelhamer, MD, FAAP
President

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

JUN 13 2007

Heinz Schneider, Dr.Med.
Vice President
Regulatory & Scientific Affairs
Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006

Dear Dr. Schneider,

This letter pertains to a citizen petition (CP), submitted to FDA on March 1, 2007, which requests that FDA take several actions related to the over-the-counter (OTC) cough and cold drug products for children under 6 years of age (see enclosed petition). As part of our review of the issues raised in this petition, we are interested in the comments and position of CHPA, in particular, on the following.

The petition questions the safety of OTC cough and cold products when used by children citing overdosing and dosing errors. Please provide us any relevant information you may have related to the ability of consumers to appropriately measure and dose children's products. We are also interested in information on the percentage of children's OTC liquid drug products sold with a dosing device (e.g. dosing cup, syringe, dropper).

The petition also raised issues related to the efficacy of cough and cold ingredients in OTC drug products and the extrapolation of adult efficacy data to children for these products. We are interested in any data that CHPA and/or your members may have on blood level measurements in children for OTC cough and cold ingredients.

If possible, we would like to receive a response to this inquiry within two months so that we can consider this information in our deliberations If you have any questions about this request, please contact Dr. Joel Schiffenbauer, Division of Nonprescription Clinical Evaluation, FDA (by phone at 301-796-1288 or by e-mail at joel.schiffenbauer@fda.hhs.gov)

The issues raised in this petition may be the subject of a future public discussion. If FDA proceeds with a public discussion, appropriate public notice and opportunity to participate will be provided.

Sincerely,

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Wyeth Consumer Healthcare
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Wyeth

Paul Bryers, Ph.D.
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August 27, 2007

Joel Schiffenbauer, MD
Deputy Director
DHHS/FDA/CDER/OND
Office of Nonprescription Products
10903 New Hampshire Avenue WO22 Stop 5411
Silver Spring MD 20993

Re: FDA request to Industry – Pediatric Information for Over-the-Counter (OTC) Cough and Cold Products

Dear Dr. Schiffenbauer:

Reference is made to your letter to Dr. Heinz Schneider (Vice President Regulatory & Scientific Affairs; Consumer Healthcare Products Association), requesting safety and efficacy information for OTC cough and cold drug products for children under 6 years of age (letter date stamped 13 June 2007).

Please find the following information from Wyeth Consumer Healthcare (WCH):

1. Ability of Consumers to Appropriately Measure and Dose Children's Products:
   No direct studies are available, however we are providing the following information:

   a) In 2004, 408 personal interviews were conducted by WCH among mothers of children aged 12 and under who had given their child an OTC remedy for the treatment of cold, flu or sinus symptoms in the previous year. Respondents were asked, "When giving your child a liquid over-the-counter medication, do you typically use the dosing cup or dropper included in the package, or do you measure it out yourself? (Record one response)." The majority indicated that they used the dosing cup/ dropper provided.

Specifically:

- 71% indicated that they used the dosing cup/dropper provided
- 26% indicated that they measured it themselves
- 3% indicated that they don't use liquids

b) A survey was recently conducted by WCH on parents of children age 2 to under 12 years old. Parents were asked: "In general, how difficult do you find it is to measure the correct dose of non prescription pediatric cold, flu or sinus medications to give to your child?" On a scale of "extremely difficult," "very difficult," "somewhat difficult," "not very difficult," and "not at all difficult," 78% of parents responded "not very difficult" or "not at all difficult."

2. Percentage of Children's OTC Liquid Drug Products Sold with Dosing Devices:

All of WCH cough and cold liquid products include a dosing device, with the exception of professional samples which are provided to parents by a healthcare professional. Listed below are the specific products of WCH that are classified as children's OTC liquid cough and cold products. Please note that the products designed for infants and toddlers are sold with oral dosing syringes, whereas the remaining products (mostly for older pediatric patients) are sold with a dosing cup.

Children's Cold Product	**Type of Dosing Device**
Robitussin Infant Cough (DM)	Syringe
Robitussin Ped. Cough & Cold	Syringe
Robitussin Ped Cough Long-Acting	Dosing cup
Robitussin Ped Cough & Cold Long-Acting	Dosing cup
Robitussin Ped Cough & Cold Night Time	Dosing cup
Dimetapp Toddler's Cold Drops	Syringe
Dimetapp Toddler's Cold & Cough Drops	Syringe
Dimetapp Cold & Allergy Elixir	Dosing cup
Dimetapp Cold & Cough DM Elixir	Dosing cup
Dimetapp Long-Acting Cough	Dosing cup
Dimetapp Night Time Flu	Dosing cup

3. Blood Levels in Children for OTC Cough and Cold Ingredients:
WCH has reviewed its files for studies that determined plasma levels of cough/cold ingredients in children. A total of five studies were identified. All five studies determined pseudoephedrine levels while 2 studies also determined chlorpheniramine levels.

Four of the studies were submitted to FDA and were reviewed as part of the applications for approved NDA 21-373 and NDA 21-587. The biopharmaceutics reviews for these applications are available at:
http://www.fda.gov/cder/foi/nda/2004/21-587_Advil_biopharmr.pdf and
http://www.fda.gov/cder/foi/nda/2002/21-373_Ibuprofen%20Pseudoephedrine_biopharmr.pdf

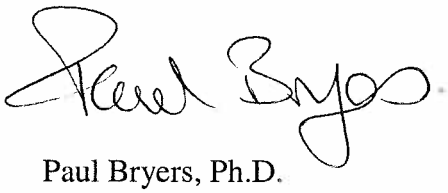
In NDA 21-587, two studies were conducted to compare the pharmacokinetic profiles of chlorpheniramine and pseudoephedrine in adults over the age of 12 years (Study AR-00-02) to children 6 to < 12 years of age (Study AR-00-03). The mean maximum plasma levels (Cmax) of pseudoephedrine in adults and children were 211.38 (± 35.5) and 194.83 (± 46.9) ng/mL, respectively. For chlorpheniramine, the mean Cmax values were 7.95 (± 1.26) ng/mL in adults and 7.34 (± 4.41) ng/mL in children. Overall, the results of these studies demonstrated that the rate and extent of absorption of pseudoephedrine and chlorpheniramine were comparable in the two age groups studied.

In NDA 21-373, two studies were conducted to compare the pharmacokinetic profiles of pseudoephedrine in children ages 2 to < 6 years (Study AQ-00-04) and in children 6 to < 12 years of age (Study AQ-99-02). The mean Cmax for pseudoephedrine in children age 2 to < 6, and children 6 to < 12 were 179.44 (± 17.07) and 218.29 (± 23.8) ng/mL, respectively. Overall, the results of these two studies demonstrated that the rate and extent of absorption of pseudoephedrine were similar across the two age groups studied. The results also suggested that the younger group had a higher clearance rate after weight normalization. For children ages 2 to < 6 and 6 to < 12, the mean (CV%) clearance rate of pseudoephedrine was 0.0308 (33.95) and 0.273 (19.48), respectively.

Finally, Study AQ-99-01 was a single-dose randomized, open-label, crossover study that characterized the pharmacokinetic profile of pseudoephedrine in children ages 6 to < 12 years of age (see attached study synopsis). The mean Cmax values for pseudoephedrine in this study were comparable to those reported in the previously mentioned studies.

If you have any questions or comments regarding this information, please contact the undersigned at (973) 660-5753, or Lauren Quinn, at (973) 660-6167.

Very truly yours,



Paul Bryers, Ph.D.
Vice President
Global Regulatory Affairs

Cc:
Dr. Charles Ganley, FDA
Dr. Heinz Schneider, CHPA

STUDY AQ-99-01
CLINICAL, PHARMACOKINETIC, AND STATISTICAL REPORT

STUDY DESIGN:	**Single-center, randomized, open-label, single-dose, two-way crossover pharmacokinetic study.**
TREATMENTS:	**IBU/PSE (Ibuprofen 200 mg/ Pseudoephedrine 30 mg) tablets and PSE (Pseudoephedrine 30 mg) tablets**
SPONSOR:	**Whitehall-Robins Healthcare Five Giralda Farms Madison, NJ 07940-0871**
STUDY DATES:	**May 8, 1999 to June 13, 1999**

This study was conducted in accordance with Good Clinical Practices.

STUDY SYNOPSIS

Title:	A Single Dose, Randomized, Open-Label, Single Center, Two-Way Crossover Pharmacokinetic Study of IBU/PSE Tablets in Children
Objective:	To characterize the rate and extent of absorption/distribution, metabolism, and elimination of pseudoephedrine in children ages 6 to <12 years following administration of a single dose of 200 mg ibuprofen plus 30 mg pseudoephedrine combination tablet or 30 mg pseudoephedrine alone tablet.
Design:	Single-center, randomized, open-label, single-dose, two-way crossover pharmacokinetic (PK) study stratified by gender.
Subjects:	Twenty-five children (12 males and 13 females) between the ages of 6 years and 11 years were enrolled. All 25 subjects received study medication and completed the study.
Treatment Regimens:	A. IBU/PSE (Ibuprofen 200 mg/Pseudoephedrine 30 mg tablet) B. PSE (Pseudoephedrine 30 mg)
Pharmacokinetic Parameters:	The following PK parameters were evaluated: area-under-the plasma concentration curve from time 0 to the last time point with detectable plasma drug concentration [AUCL], area–under-the-plasma concentration time curve from time 0 to infinity [AUCI], peak plasma concentration [C_{max}], time-to-peak plasma concentration [T_{max}], mean residence time [MRT], half-life ($t_{½}$), elimination rate (kel), volume of distribution (Vd), and clearance (C1).
Statistical Methods:	Pharmacokinetic parameters AUCL, AUCI, and C_{max} were analyzed. AUCL was considered the primary PK parameter. The other PK parameters are summarized. AUCL, AUCI, C_{max}, (both log transformed and untransformed) were analyzed for differences between treatments using an analysis of variance with effects for gender, subject (gender), period, treatment, and treatment-by-gender interaction. As per FDA requirements, a 90% two-sided confidence interval for the bioavailability, relative to the reference, based on the least square means (equivalent to two one-sided t-tests) was calculated for AUCL, AUCI, and C_{max}. For each of the above comparisons, bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 0.80 and 1.25 for log transformed PK parameters or between 0.80 and 1.20 for untransformed PK parameters. The log-transformed analyses were considered primary. Adverse experiences were tabulated.

Results:

Subject Disposition: Twenty-five subjects were enrolled in the study and completed both study periods. All 25 subjects were included in the analysis of pharmacokinetic parameters.

Demographics: The mean age of the study population was 8.0 ± 1.74 years (range: 6 - 11 years). Twelve (48%) were male and 13 (52%) were female. The mean height was 52.0 ± 4.6 inches (range: 45 - 60 inches) and the mean weight was 66.2 ± 16.04 pounds (range 46 - 109 pounds). 92% of the subjects were Caucasian, 4% were Black and 4% were Other.

Pharmacokinetics: Key pseudoephedrine PK parameters are summarized in Table S.1. The mean plasma concentration versus time curve for pseudoephedrine is shown in Figure S.1.

Safety: Both treatments were well tolerated. There were no deaths or serious adverse experiences reported in the study. No subject discontinued from the study due to an adverse experience.

Conclusion:

The results indicate that IBU/PSE tablets had an equivalent rate and extent of absorption of pseudoephedrine relative to the single entity marketed product containing pseudoedphedrine (PSE tablets). There was no pharmacokinetic interaction between ibuprofen and pseudoephedrine. Pseudoephedrine was well tolerated, whether taken alone or in combination with ibuprofen.

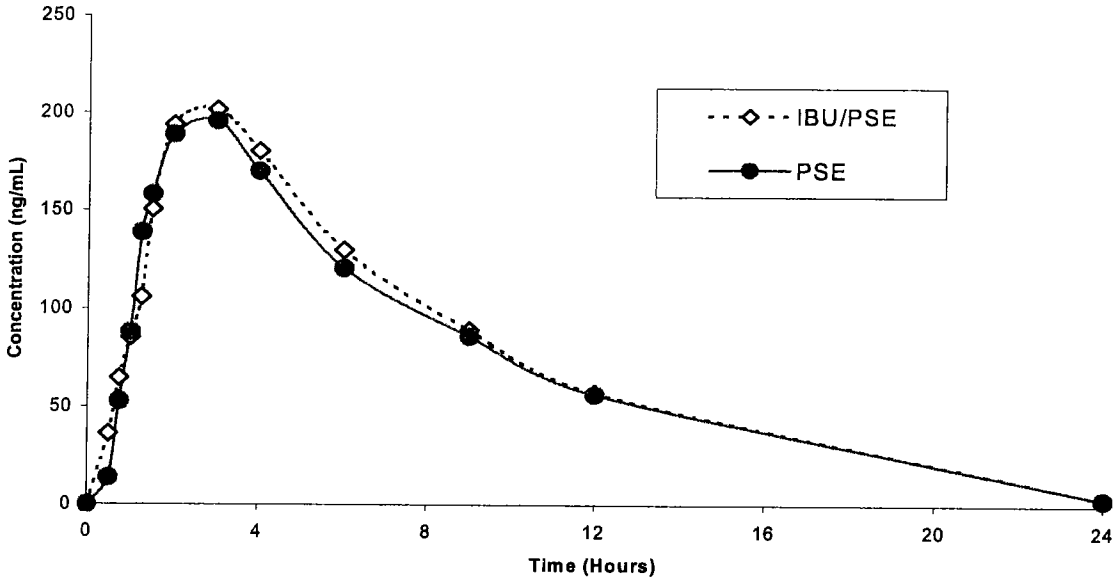
Table S.1: Summary of Results - Pseudoephedrine Pharmacokinetic Parameters: 25 Subjects

(Mean ± Standard Deviation)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	T ½ (h)
IBU/PSE Tab. (A)	1565.7 (530.5)	1859.0 (611.3)	265.8 (86.8)	2.2 (1.0)	4.6 (1.0)
PSE Tab. (B) †	1510.5 (561.1)	1791.9 (526.2)	236.0 (72.5)	2.3 (0.9)	4.7 (0.6)
A/B Ratio (%)^	103.2	101.5	111.9	-	-
A/B 90% CI^	95.2-112.0	93.1-110.8	104.9-119.4	-	-

† Reference product ^Based on log-transformed data.
CI = confidence interval

Figure S.1: Mean Pseudoephedrine Plasma Concentration over Time



Wyeth Consumer Healthcare
Five Giralda Farms
Madison, NJ 07940

Paul Bryers, Ph.D.
Vice President, Global Regulatory Affairs
Phone: 973 660-5753
Fax: 973-660-7187
bryersp@wyeth.com

Wyeth

August 27, 2007

Joel Schiffenbauer, MD
Deputy Director
DHHS/FDA/CDER/OND
Office of Nonprescription Products
10903 New Hampshire Avenue WO22 Stop 5411
Silver Spring MD 20993

Re: FDA request to Industry – Pediatric Information for Over-the-Counter (OTC) Cough and Cold Products

Dear Dr. Schiffenbauer:

Reference is made to your letter to Dr. Heinz Schneider (Vice President Regulatory & Scientific Affairs; Consumer Healthcare Products Association), requesting safety and efficacy information for OTC cough and cold drug products for children under 6 years of age (letter date stamped 13 June 2007).

Please find the following information from Wyeth Consumer Healthcare (WCH):

1. Ability of Consumers to Appropriately Measure and Dose Children's Products:
   No direct studies are available, however we are providing the following information:

   a) In 2004, 408 personal interviews were conducted by WCH among mothers of children aged 12 and under who had given their child an OTC remedy for the treatment of cold, flu or sinus symptoms in the previous year. Respondents were asked, "When giving your child a liquid over-the-counter medication, do you typically use the dosing cup or dropper included in the package, or do you measure it out yourself? (Record one response)." The majority indicated that they used the dosing cup/ dropper provided.

Specifically:

- 71% indicated that they used the dosing cup/dropper provided
- 26% indicated that they measured it themselves
- 3% indicated that they don't use liquids

b) A survey was recently conducted by WCH on parents of children age 2 to under 12 years old. Parents were asked: "In general, how difficult do you find it is to measure the correct dose of non prescription pediatric cold, flu or sinus medications to give to your child?" On a scale of "extremely difficult," "very difficult," "somewhat difficult," "not very difficult," and "not at all difficult," 78% of parents responded "not very difficult" or "not at all difficult."

2. Percentage of Children's OTC Liquid Drug Products Sold with Dosing Devices:

All of WCH cough and cold liquid products include a dosing device, with the exception of professional samples which are provided to parents by a healthcare professional. Listed below are the specific products of WCH that are classified as children's OTC liquid cough and cold products. Please note that the products designed for infants and toddlers are sold with oral dosing syringes, whereas the remaining products (mostly for older pediatric patients) are sold with a dosing cup.

Children's Cold Product	Type of Dosing Device
Robitussin Infant Cough (DM)	Syringe
Robitussin Ped. Cough & Cold	Syringe
Robitussin Ped Cough Long-Acting	Dosing cup
Robitussin Ped Cough & Cold Long-Acting	Dosing cup
Robitussin Ped Cough & Cold Night Time	Dosing cup
Dimetapp Toddler's Cold Drops	Syringe
Dimetapp Toddler's Cold & Cough Drops	Syringe
Dimetapp Cold & Allergy Elixir	Dosing cup
Dimetapp Cold & Cough DM Elixir	Dosing cup
Dimetapp Long-Acting Cough	Dosing cup
Dimetapp Night Time Flu	Dosing cup

3. Blood Levels in Children for OTC Cough and Cold Ingredients:
WCH has reviewed its files for studies that determined plasma levels of cough/cold ingredients in children. A total of five studies were identified. All five studies determined pseudoephedrine levels while 2 studies also determined chlorpheniramine levels.

Four of the studies were submitted to FDA and were reviewed as part of the applications for approved NDA 21-373 and NDA 21-587. The biopharmaceutics reviews for these applications are available at:
http://www.fda.gov/cder/foi/nda/2004/21-587_Advil_biopharmr.pdf and
http://www.fda.gov/cder/foi/nda/2002/21-373_Ibuprofen%20Pseudoephedrine_biopharmr.pdf

In NDA 21-587, two studies were conducted to compare the pharmacokinetic profiles of chlorpheniramine and pseudoephedrine in adults over the age of 12 years (Study AR-00-02) to children 6 to < 12 years of age (Study AR-00-03). The mean maximum plasma levels (Cmax) of pseudoephedrine in adults and children were 211.38 (± 35.5) and 194.83 (± 46.9) ng/mL, respectively. For chlorpheniramine, the mean Cmax values were 7.95 (± 1.26) ng/mL in adults and 7.34 (± 4.41) ng/mL in children. Overall, the results of these studies demonstrated that the rate and extent of absorption of pseudoephedrine and chlorpheniramine were comparable in the two age groups studied.

In NDA 21-373, two studies were conducted to compare the pharmacokinetic profiles of pseudoephedrine in children ages 2 to < 6 years (Study AQ-00-04) and in children 6 to < 12 years of age (Study AQ-99-02). The mean Cmax for pseudoephedrine in children age 2 to < 6, and children 6 to < 12 were 179.44 (± 17.07) and 218.29 (± 23.8) ng/mL, respectively. Overall, the results of these two studies demonstrated that the rate and extent of absorption of pseudoephedrine were similar across the two age groups studied. The results also suggested that the younger group had a higher clearance rate after weight normalization. For children ages 2 to < 6 and 6 to < 12, the mean (CV%) clearance rate of pseudoephedrine was 0.0308 (33.95) and 0.273 (19.48), respectively.

Finally, Study AQ-99-01 was a single-dose randomized, open-label, crossover study that characterized the pharmacokinetic profile of pseudoephedrine in children ages 6 to < 12 years of age (see attached study synopsis). The mean Cmax values for pseudoephedrine in this study were comparable to those reported in the previously mentioned studies.

If you have any questions or comments regarding this information, please contact the undersigned at (973) 660-5753, or Lauren Quinn, at (973) 660-6167.

Very truly yours,

Paul Bryers, Ph.D.
Vice President
Global Regulatory Affairs

Cc:
Dr. Charles Ganley, FDA
Dr. Heinz Schneider, CHPA

STUDY AQ-99-01
CLINICAL, PHARMACOKINETIC, AND STATISTICAL REPORT

STUDY DESIGN:	**Single-center, randomized, open-label, single-dose, two-way crossover pharmacokinetic study.**
TREATMENTS:	**IBU/PSE (Ibuprofen 200 mg/ Pseudoephedrine 30 mg) tablets and PSE (Pseudoephedrine 30 mg) tablets**
SPONSOR:	**Whitehall-Robins Healthcare Five Giralda Farms Madison, NJ 07940-0871**
STUDY DATES:	**May 8, 1999 to June 13, 1999**

This study was conducted in accordance with Good Clinical Practices.

STUDY SYNOPSIS

Title:	A Single Dose, Randomized, Open-Label, Single Center, Two-Way Crossover Pharmacokinetic Study of IBU/PSE Tablets in Children
Objective:	To characterize the rate and extent of absorption/distribution, metabolism, and elimination of pseudoephedrine in children ages 6 to <12 years following administration of a single dose of 200 mg ibuprofen plus 30 mg pseudoephedrine combination tablet or 30 mg pseudoephedrine alone tablet.
Design:	Single-center, randomized, open-label, single-dose, two-way crossover pharmacokinetic (PK) study stratified by gender.
Subjects:	Twenty-five children (12 males and 13 females) between the ages of 6 years and 11 years were enrolled. All 25 subjects received study medication and completed the study.
Treatment Regimens:	A. IBU/PSE (Ibuprofen 200 mg/Pseudoephedrine 30 mg tablet) B. PSE (Pseudoephedrine 30 mg)
Pharmacokinetic Parameters:	The following PK parameters were evaluated: area-under-the plasma concentration curve from time 0 to the last time point with detectable plasma drug concentration [AUCL], area–under-the-plasma concentration time curve from time 0 to infinity [AUCI], peak plasma concentration [C_{max}], time-to-peak plasma concentration [T_{max}], mean residence time [MRT], half-life ($t_{½}$), elimination rate (kel), volume of distribution (Vd), and clearance (C1).
Statistical Methods:	Pharmacokinetic parameters AUCL, AUCI, and C_{max} were analyzed. AUCL was considered the primary PK parameter. The other PK parameters are summarized. AUCL, AUCI, C_{max}, (both log transformed and untransformed) were analyzed for differences between treatments using an analysis of variance with effects for gender, subject (gender), period, treatment, and treatment-by-gender interaction. As per FDA requirements, a 90% two-sided confidence interval for the bioavailability, relative to the reference, based on the least square means (equivalent to two one-sided t-tests) was calculated for AUCL, AUCI, and C_{max}. For each of the above comparisons, bioequivalence was declared if the 90% two-sided confidence interval for the ratio was between 0.80 and 1.25 for log transformed PK parameters or between 0.80 and 1.20 for untransformed PK parameters. The log-transformed analyses were considered primary. Adverse experiences were tabulated.

Results:

Subject Disposition: Twenty-five subjects were enrolled in the study and completed both study periods. All 25 subjects were included in the analysis of pharmacokinetic parameters.

Demographics: The mean age of the study population was 8.0 ± 1.74 years (range: 6 - 11 years). Twelve (48%) were male and 13 (52%) were female. The mean height was 52.0 ± 4.6 inches (range: 45 - 60 inches) and the mean weight was 66.2 ± 16.04 pounds (range 46 - 109 pounds). 92% of the subjects were Caucasian, 4% were Black and 4% were Other.

Pharmacokinetics: Key pseudoephedrine PK parameters are summarized in Table S.1. The mean plasma concentration versus time curve for pseudoephedrine is shown in Figure S.1.

Safety: Both treatments were well tolerated. There were no deaths or serious adverse experiences reported in the study. No subject discontinued from the study due to an adverse experience.

Conclusion:

The results indicate that IBU/PSE tablets had an equivalent rate and extent of absorption of pseudoephedrine relative to the single entity marketed product containing pseudoedphedrine (PSE tablets). There was no pharmacokinetic interaction between ibuprofen and pseudoephedrine. Pseudoephedrine was well tolerated, whether taken alone or in combination with ibuprofen.

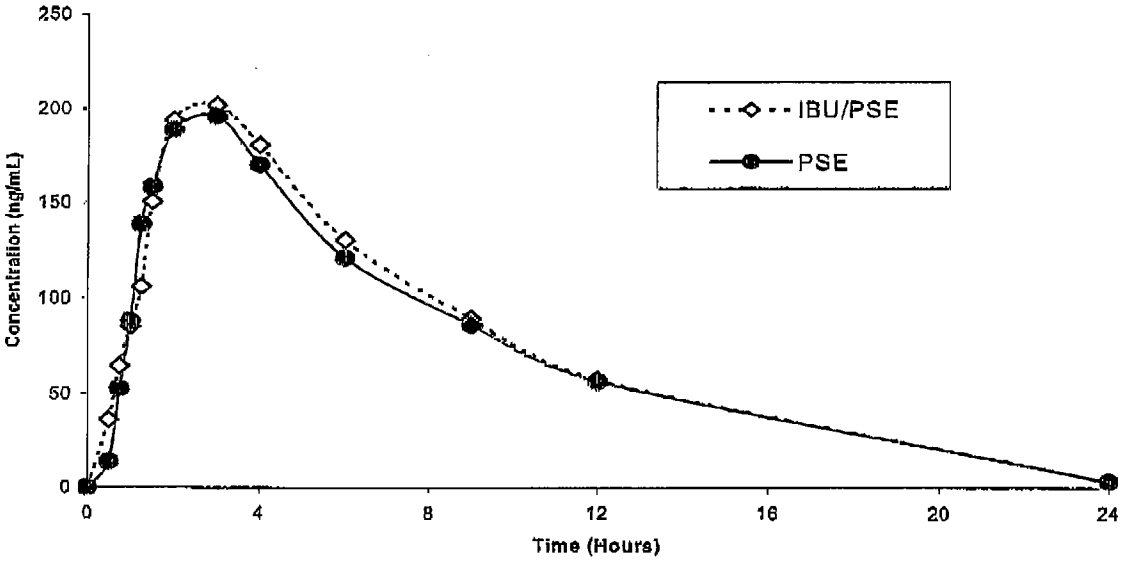
Table S.1: Summary of Results - Pseudoephedrine Pharmacokinetic Parameters: 25 Subjects

(Mean ± Standard Deviation)

Treatment	AUCL (ng•h/mL)	AUCI (ng•h/mL)	Cmax (ng/mL)	Tmax (h)	T ½ (h)
IBU/PSE Tab. (A)	1565.7 (530.5)	1859.0 (611.3)	265.8 (86.8)	2.2 (1.0)	4.6 (1.0)
PSE Tab. (B) †	1510.5 (561.1)	1791.9 (526.2)	236.0 (72.5)	2.3 (0.9)	4.7 (0.6)
A/B Ratio (%)^	103.2	101.5	111.9	-	-
A/B 90% CI^	95.2-112.0	93.1-110.8	104.9-119.4	-	-

† Reference product ^Based on log-transformed data.
CI = confidence interval

Figure S.1: Mean Pseudoephedrine Plasma Concentration over Time



CHPA

founded 1881

August 31, 2007

Joel Schiffenbauer, MD
Deputy Director
DHHS/FDA/CDER/OND
Office of Nonprescription Products
10903 New Hampshire Avenue
WO22 Stop 5411
Silver Spring, MD 20993

Re: FDA Request to Industry – Pediatric Information for Over-the-Counter (OTC) Cough and Cold Products

Dear Dr. Schiffenbauer:

Reference is made to your letter dated 13 June 2007 addressed to me requesting safety and efficacy information for OTC cough and cold drug products for children under 6 years of age.

Please find the following information from the Consumer Healthcare Products Association (CHPA):

1. Ability of Consumers to Appropriately Measure and Dose Children's Products

   In a qualitative study conducted for CHPA consisting of over 60 one-on-one interviews with the primary caregiver for children under 6 years of age no issues of confusion arose concerning use of dosing devices for liquid products. A report on the findings will be forthcoming.

Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006
t 202.429.9260 f 202.223.6835
www.chpa-info.org

2. Percentage of Children's OTC Liquid Drug Products Sold with Dosing Devices

Using information and estimates provided by Information Resources, Inc., there were approximately 41 million units of pediatric cough and cold products sold in the 52 weeks ending July 15, 2007.

This includes approximate dosage form percentages of:

Liquid (not concentrated):	63%
Chewable:	3%
Drops (ie, concentrated liquid):	19%
Powder:	3.5%
Strip:	11%
(Others:	less than 0.5 %)

Notes:

(1) These estimates cover retail sales in the food, drug, and mass channels of trade, excluding Wal-Mart. (Wal-Mart does not publish category sales estimates.)
(2) These estimates include national brands and store brands.
(3) Because many products are labeled for use by both adults and children, these estimates include product forms generally intended for use by children under 12. Adult labeling may still be present. Conversely, product forms generally intended for adults, but where labeling for children may still be present, are not included. 'Product forms' refers to product breakdowns at the level above an individual size – i.e., Brand X Cough & Sore Throat, liquid, grape [pain reliever/fever reducer (acetaminophen), cough suppressant (dextromethorphan)].

A large majority of product forms generally intended for use by children in liquid form (concentrated or otherwise) include a dosing cup, dropper, or syringe. While we are unable to provide a more precise estimate, we are not aware of any concentrated drops made by CHPA members that do not include a dropper or syringe. For all liquids (concentrated drops or otherwise), a minimum of 87% of products in the estimate include a dosing cup, dropper, or syringe. A maximum of 94.5% of products in the estimate include a dosing cup, dropper, or syringe.

3. Blood Levels for OTC Cough and Cold Ingredients in Children

Our efforts to respond to the agency's request were twofold: (1) we contacted CHPA member companies and asked them to provide pertinent data either to us or directly to FDA, and (2) we conducted a search of MEDLINE from 1966 through July 2007.

We identified 8 studies with pharmacokinetic (PK) data in children (see copies of publications in the attachment to this letter). All data were published in scientific journals, but only a poster abstract is available for one of the studies (*Auritt et al. 1981*). Study design and PK characteristics determined in the pediatric studies are presented in Tables 1 – 5 in the Appendix to this letter. One study each with pseudoephedrine and diphenhydramine include PK

comparisons between children and adults (*Auritt et al. 1981, Simons et al. 1990*). The remaining 6 studies investigated the PK profile in children only for dextromethorphan (*Schmitt et al. 1997*), pseudoephedrine (*Simons et al. 1996*), brompheniramine (*Simons et al. 1999)* and chlorpheniramine (*Thompson et al. 1981, Simons et al. 1982b, Simons et al. 1984*). The latter studies were complemented by PK data from 4 studies in adults with a design comparable to the corresponding pediatric studies in terms of dosage form and duration of treatment (*Woodworth et al. 1987, Williams et al. 1984, Simons et al. 1982a, Kotzan et al. 1982*).

Please do not hesitate to contact me if you have any questions or comments.

Sincerely,

Heinrich Schneider, Dr.Med.
Vice President, Regulatory & Scientific Affairs
T 202-429-3535
hschneider@chpa-info.org

Appendix (List of Publications, Tables 1 – 5)

Attachments (Copies of 12 publications)

APPENDIX

PEDIATRIC PK STUDIES

Dextromethorphan

- *Schmitt B, Bauersfeld U, Fanconi S, Wohlrab G, Huisman TA, Bandtlow C, Baumann P, Superti-Furga A, Martin E, Arbenz U, Molinari L, Turina M, Boltshauser E, Schmid ER. The effect of the N-methyl-D-aspartate receptor antagonist dextromethorphan on perioperative brain injury in children undergoing cardiac surgery with cardiopulmonary bypass: results of a pilot study. Neuropediatrics 1997; 28:191-7.*

Pseudoephedrine

- *Simons FE, Gu X, Watson WT, Simons KJ. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. J Pediatr. 1996; 129:729-34.*
- *Auritt WA, Saccar CL, Handfinger MG, Mansmann HC, Yaffe SJ, Warren JT, Welch RM, Findlay WA. Pharmacokinetics of pseudoephedrine in children. Ann Allergy 1981: 47139.*

Diphenhydramine

- *Simons KJ, Watson WT, Martin TJ, Chen XY, Simons FE. Diphenhydramine: pharmacokinetics and pharmacodynamics in elderly adults, young adults, and children. J Clin Pharmacol. 1990; 30:665-71.*

Brompheniramine

- Simons FE, Roberts JR, Gu X, Kapur S, Simons KJ. The clinical pharmacology of brompheniramine in children. J Allergy Clin Immunol. 1999; 103:223-6.

Chlorpheniramine

- *Thompson JA, Bloedow DC, Leffert FH. Pharmacokinetics of intravenous chlorpheniramine in children. J Pharm Sci.* 1981; 70:1284-6.
- *Simons FE, Luciuk GH, Simons KJ. Pharmacokinetics and efficacy of chlorpheniramine in children. J Allergy Clin Immunol. 1982; 69:376-81.*
- *Simons KJ, Simons FE, Luciuk GH, Frith EM. Urinary excretion of chlorpheniramine and its metabolites in children. J Pharm Sci. 1984; 73:595-9.*

ADULT PK STUDIES

Dextromethorphan

- *Woodworth JR, Dennis SR, Hinsvark ON, Amsel LP, Rotenberg KS. Bioavailability evaluation of a controlled-release dextromethorphan liquid. J Clin Pharmacol. 1987; 27:133-8.*

Pseudoephedrine

- *Williams BO, Liao SH, Lai AA, Arnold JD, Perkins JG, Blum MR, Findlay JW. Bioavailability of pseudoephedrine and triprolidine from combination and single-ingredient products. Clin Pharm. 1984; 3:638-43.*

Brompheniramine

- *Simons FE, Frith EM, Simons KJ. The pharmacokinetics and antihistaminic effects of brompheniramine. J Allergy Clin Immunol. 1982; 70:458-64.*

Chlorpheniramine

- *Kotzan JA, Vallner JJ, Stewart JT, Brown WJ, Viswanathan CT, Needham TE, Dighe SV, Malinowski R. Bioavailability of regular and controlled-release chlorpheniramine products. J Pharm Sci. 1982; 71:919-23.*

Table 1. 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**	
Results:	**Children***		**Adults****	
	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.

Table 2. 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

Table 3. 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
t_{max} *(hr)*	1.3 ± 0.5	1.7 ± 1.0	1.7 ± 0.8
C_{max} *(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

Table 4. 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
t_{max} *(hr)*	3.2 ± 0.3	3.1 ± 1.1
C_{max} *(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

Table 5. 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*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

AUG 7 2007

Dean Wilkerson, MBA, JD, CAE
Executive Director
American College of Emergency Physicians
P.O. Box 619911
Dallas, TX 75261-9911

Dear Dr. Wilkerson,

This letter pertains to a citizen petition, submitted to FDA on March 1, 2007, which requests that FDA take several actions related to the over-the-counter (OTC) cough and cold drug products for children under 6 years of age (see enclosed petition). In order to consider and address the issues raised in this petition, we are interested in comments the American College of Emergency Physicians (ACEP) may have on any of the issues as outlined below.

1. The petition proposes that the labeling of the cough and cold products include the following statements: "These products have not been found to be safe or effective in children under 6 years of age for treatment of cough and cold. These products should not be used for treatment of cough and cold in children under 6 years of age."

   We are interested in the opinion of the ACEP on labeling that would be appropriate for OTC cough and cold drug products for children.

   Please describe what impact, if any, you anticipate labeling changes, such as the ones proposed in the petition, would have on emergency physicians' decision to prescribe cough and cold medications for children under 6 years of age.

2. The petition cites several references that describe clinical efficacy studies in children. The petition concludes that these studies demonstrate that the OTC cough and cold drug products are not effective for treatment of cough or cold symptoms in children. Conducting successful clinical efficacy studies in children with symptoms of cold or allergic rhinitis has been difficult due, in large part, to the limited ability of children to subjectively quantify the severity of their symptoms. Because of this, FDA has extrapolated efficacy data from adults to children, not only in the OTC monograph for cold and cough drug products, but also for the approval of pediatric indications for NDA products when the studies conducted in children failed to establish a significant effect of active therapy over placebo.

   a. Do you have comments on the use of extrapolation of efficacy data from adults to children in general and for OTC cough and cold products specifically?

If possible, we would like to receive a response to this inquiry by September 10, 2007, so that we can incorporate your comments in our deliberations. If you have any questions about this request, please contact Dr. Joel Schiffenbauer, Division of Nonprescription Clinical Evaluation, FDA (by phone at 301-796-1288 or by e-mail at joel.schiffenbauer@fda.hhs.gov)

The issues raised in this petition may be the subject of a future public discussion. If FDA proceeds with a public discussion, appropriate public notice and opportunity to participate will be provided.

Sincerely,

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research