

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 overdose 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

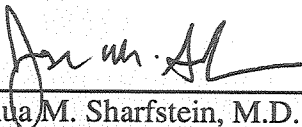
According to 21 CFR Sec. 25.31(a), this Petition qualifies for a categorical exclusion from the requirement that an environmental impact statement be submitted.

ECONOMIC IMPACT STATEMENT

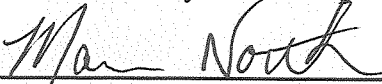
According to 21 CFR Sec 10.30(b), an economic impact statement is to be submitted only when requested by the Commissioner following reviewing of this Petition.

CERTIFICATION

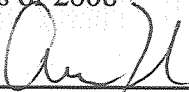
The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.



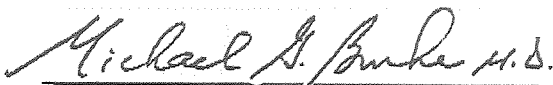
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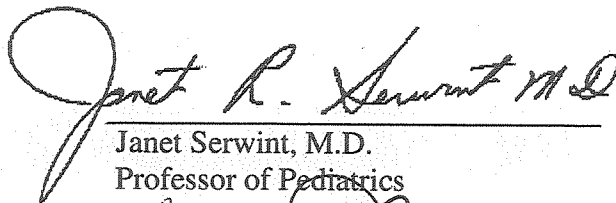
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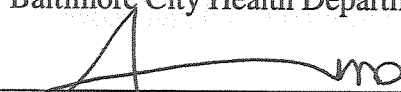
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VI. NOTES

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