

May 2, 2007

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

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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

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.

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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 preparations 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. Maturation 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.

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 administration 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}

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 medications. *Pediatrics* 2001;**108**(3):e52.

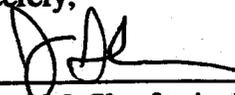
¹² Litovitz T, Manoguerra A. Comparison of Pediatric Poisoning Hazards: An Analysis of 3.8 Million Exposure Incidents. A Report from the American Association of Poison Control Centers. *Pediatrics* 1992;**89**(6 Pt 1): 999-1006.

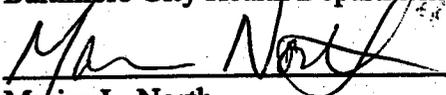
¹³ Centers for Disease Control and Prevention. Infant Deaths Associated with Cough and Cold Medications --- Two States, 2005. *MMWR* 2007 Jan 12;**56**(01):1-4.

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>.

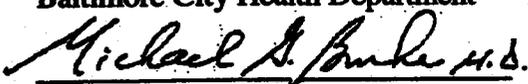
We urge the agency to act quickly.

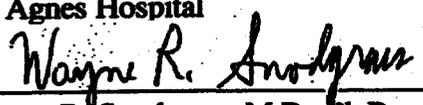
Sincerely,

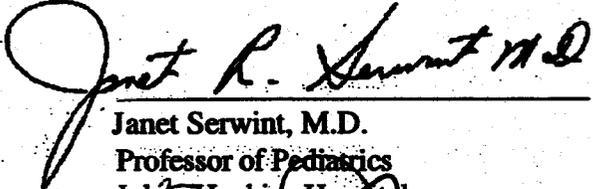

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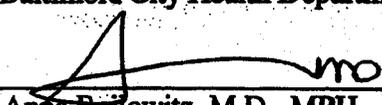

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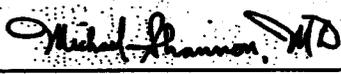

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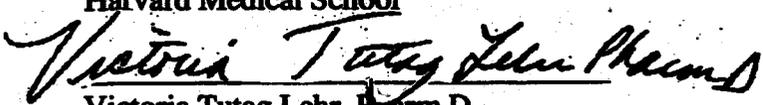

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