

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA2008N0466]

Over the Counter Cough and Cold Medications for Pediatric Use; Notice of Public Hearing

AGENCY:

Food and Drug Administration, HHS.

ACTION:

Notice of public hearing; request for comments.

SUMMARY:

The Food and Drug Administration (FDA) is announcing a public hearing to obtain input regarding over-the-counter (OTC) cough and cold drugs marketed for pediatric use. Many of these nonprescription cough and cold drug products are marketed under the OTC Drug Review, which established a monograph describing the conditions under which certain OTC ingredients are considered to be generally recognized as safe and effective. Recently, safety and efficacy concerns have been raised regarding the pediatric dosing and use of certain active ingredients in OTC cough and cold drug products. FDA is developing a proposed rule to revise the pediatric labeling contained in the Final Monograph for Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use. At this public hearing, FDA is interested in obtaining public comment about certain scientific, regulatory, and product use issues as it proceeds with the rulemaking and reviews new drug applications (NDAs) for these ingredients.

Dates and Times: The public hearing will be held on October 2, 2008, from 8 a.m. to 5 p.m.

Location: The public hearing will be held at the Sheraton Washington North Hotel, 4095 Powder Mill Rd., Beltsville, MD 20705.

ADDRESSES:

Submit written registration and written comments to the Division of Dockets Management (HFA305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic registration to <http://www.regulations.gov>.

Submit electronic comments to <http://www.regulations.gov>. All comments should be identified with the docket number found in brackets in the heading of this document.

Transcripts of the hearing will be available for review at the Division of Dockets Management and on the Internet at <http://www.regulations.gov>

approximately 30 days after the hearing.

For Registration to Attend and/or Participate in the Hearing:

Seating at the hearing is limited. People interested in attending should submit written or electronic registration to the Division of Docket Management (see ADDRESSES) by close of business on September 15, 2008. Registration is free and will be on a first-come, first-served basis. Written or electronic comments will be accepted until December 2, 2008.

If you wish to make an oral presentation at the hearing, you must state your intention on your registration submission (see ADDRESSES). To speak, submit your name, title, business affiliation, address, telephone and fax numbers, and e-mail address. FDA has included questions for comment in section II of this document. You should also identify by number each question you wish to address in your presentation. FDA will do its best to accommodate requests to speak. Individuals and organizations with common interests are urged to consolidate or coordinate their presentations, and to request time for a joint presentation. FDA will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin.

If you need special accommodations because of a disability, please inform Faith Dugan, (see For Information on the Hearing Contact).

For Information on the Hearing Contact: Faith Dugan, Food and Drug Administration, 5600 Fishers Lane, rm. 14101, Rockville, MD 20857, 3017963446, FAX: 3018474752, e-mail: Faith.Dugan@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

On March 1, 2007, FDA received a citizen petition submitted by a number of pediatric health care practitioners that raised concerns about the safety and efficacy of OTC cough and cold products in children less than 6 years old. The petition requested that FDA, among other actions, amend the OTC drug monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (CCABADP) in 21 CFR part 341 to revise the labeling for OTC antitussive, expectorant, nasal decongestant, antihistamine, and combination cough and cold products. The petition requested that revised labeling state that these products should not be used in children under 6 years of age for the treatment of cough and cold because the products have not been found to be safe or effective. In addition, the petition requested that the agency notify manufacturers of products whose labeling either uses such terms as infant or baby, or displays images of children under the age of 6, that such marketing is not supported by scientific evidence and that manufacturers will be subject to enforcement action at any time. The petition and additional information can be found at the following Web site:
<http://www.fda.gov/ohrms/dockets/dockets/07p0074/07p0074.htm>.

Many of today's OTC cough and cold medicines are marketed under monographs established through the OTC Drug Review and published in the Code of Federal Regulations. FDA initiated the OTC Drug Review in 1972, after amendments to the Federal Food, Drug, and Cosmetic Act in 1962 required that drugs be shown to be effective as well as safe. Using expert advisory panels to review data, the OTC

Drug Review examined drug ingredients marketed OTC in the United States to verify which of these ingredients can be generally recognized among qualified experts as safe and effective for their intended uses (GRAS/E). After review by the panel, FDA published advance notices of proposed rulemaking for active ingredients in various therapeutic categories to establish monographs describing the conditions under which the products could be considered GRAS/E and marketed under the monograph without an approved new drug application. Based on the recommendations in the panel reports and additional public comments and data, FDA published a proposed rule, also known as a tentative final monograph (TFM), which set forth the FDA's views on the conditions of use for the monograph. Finally, based on additional comments and information submitted in response to the TFM, FDA published final monographs. The final monographs, codified in the Code of Federal Regulations, specify the active ingredients that are GRAS/E for each indication, and for each such active ingredient, the permitted dosages, claims, and warnings. Products that comply with all specified monograph conditions may be marketed without prior FDA approval.

Through the OTC Drug Review, FDA has established numerous monographs for classes of OTC drug ingredients. Each completed OTC drug monograph considers a particular therapeutic class of drugs (e.g., antacids, topical antifungal drugs, nighttime sleep aids) and describes the active ingredients that have been determined to be GRAS/E through the OTC Drug Review process, with specifications for the amount of drug per dose, labeling, and other general requirements. As long as a manufacturer uses ingredients (or combinations of ingredients) that are included in the monograph, and follows the monograph specifications in manufacturing and marketing, these OTC Monograph products may be sold over the counter without FDA pre-clearance. Drugs that are not covered under the OTC Drug Review may be marketed OTC under the terms of an approved NDA.

In the Federal Register of September 9, 1976 (41 FR 38312), FDA published an advance notice of proposed rulemaking (ANPRM) to establish a monograph under 330.10(a)(6) (21 CFR 330.10(a)(6)), for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products. At the same time, FDA published the recommendations of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Panel), which was the advisory review panel that evaluated these products.

The final CCABADP monograph includes GRAS/E active ingredients in five separate categories: Antihistamines (13 active ingredients), decongestants (13 active ingredients), antitussives (10 active ingredients), bronchodilator (7 active ingredients), and expectorants (1 active ingredient).¹

¹The FDA issued the tentative final monograph for single ingredient OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products in segments, over a 3-year period. The first segment, on anticholinergic drug product and expectorant drug products, was published in the Federal Register of July 9, 1982 (47 FR 30002). The second segment, on bronchodilator drug products, was published in the Federal Register of October 26, 1982 (47 FR 47520). The third segment, on antitussive drug products, was published in the Federal Register of October 19, 1983 (48 FR 48576). The fourth and fifth segments, on nasal decongestant drug products and antihistamine drug products, were published in the Federal Register of January 15, 1985 (50 FR 2200 and 50 FR 2220). The agency's tentative final monograph for OTC cough-cold combination drug products was published in the Federal Register of August 12, 1988 (53 FR 30522). Final monographs for these OTC drug products also were published in segments between

1985 and 1994: Anticholinergic (50 FR 46582, November 8, 1985); bronchodilator (51 FR 35326, October 2, 1986); antitussive (52 FR 30042, August 12, 1987); expectorant (54 FR 8494, February 28, 1989); antihistamine (57 FR 58356, December 9, 1992); nasal decongestant (59 FR 43386, August 23, 1994); and combination products (67 FR 78158, December 23, 2002).

Dosing for each active ingredient was largely based on the advisory panel recommendations, made in consultation with the Special Panel on Pediatric Dosage. The following statements appear in the ANPRM:

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The dosage that will produce optimum therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age, weight and metabolic, pathological, or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered general guides.

Definitive pediatric drug dosage should be derived from data obtained in clinical trials with children using protocols similar to those used in adult patients. The Panel recognizes the extreme difficulties attendant upon such trials but also recognizes the immediate need to make recommendations for pediatric dosage pending availability of such definitive data.

Traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the usual adult dose. Dosage calculated on the basis of the age of the child, although convenient, may be the least reliable method because of the large variation in the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the Panel has concluded that dosage recommendations based on age are the most reasonable since they would be most easily understood by the consumer * * *.

Unless indicated contrarily, the Panel recommends the following guidelines for determining safe and effective pediatric dosages for the individual [CCABADP] ingredients discussed in this document: 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 differences between children under 2 years of age, and other age groups with respect to the anatomy and physiology disorders of their respiratory system, their responses to diseases affecting the respiratory system, and their responses to drugs make general labeling restrictions for this age group essential. For example, infants because of the smaller diameter of their respiratory airways are particularly prone to the complications of respiratory distress during an acute respiratory tract infection such as may occur in the common cold. Therefore, parents of children under 2 years of age should be advised to consult a physician for diagnosis and individualized therapeutic recommendations, even for symptoms and conditions that are considered appropriate for self-medication in older children and adults. Because of these considerations, the Panel recommends that the general labeling of [CCABADP] products for use in children under 2 years of age requires the advice and supervision of a physician * * *.

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41 FR 38312; 38333 (September 9, 1976).

We estimate that there are approximately 10,000 products being marketed for cold, cough, or combined indications under the OTC Drug Review. (See 67 FR 78158 at 78166.) Depending on the dosage form and strength of these products, many of them are labeled for pediatric use, including some that are labeled for use in both adults and children. There are approximately 38 active ingredients in the final CCABADP monograph. Some combination cough and cold products contain as many as four of these active ingredients in a single dosage form, meaning that patients may be exposed to four different active ingredients when using a single product. From 2002 to 2006, there were approximately 36 billion units of combination cough and cold products sold each year in the United States. For liquid formulations used for the youngest children, there were approximately 190 million units sold each year in the combined cough and cold categories during this period.²<FTREF/>

²Transcript of joint meeting of the Nonprescription Drug Advisory Committee and the Pediatric Advisory Committee, October 18, 2007, p. 10.

During the past decade, there have been several important new developments in the evaluation of safety and efficacy of drugs for pediatric use. First, the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105115) (Nov. 21, 1997) was enacted, and included a provision to create voluntary incentives to develop medications for use in the pediatric population. This program was reauthorized and expanded first in the Best Pharmaceuticals for Children Act of 2002 (Public Law 107109) (January 4, 2002), and then again in Title V of the FDA Amendments Act of 2007 (FDAAA) (Public Law 11085) (September 27, 2007). The Pediatric Research Equity Act (PREA) of 2003 required that drugs be studied in pediatric patients in certain circumstances. The PREA requirements were reauthorized and expanded by Title IV of FDAAA in 2007. Collectively, these laws recognize that differences in metabolism between adults and children, as well as differences between pediatric age groups, may require individualized dosing. They also recognize that there are often differences in effects of drugs and in adverse events observed in pediatric patients when compared to adult patients. Although these laws do not apply to products marketed under an OTC monograph, data from studies performed under these provisions suggest that children are not small adults, but rather may have a response to medication, both beneficial and adverse, that is different from adults.

Given the evolution in our thinking about the use of drugs in children, the passage of more than 30 years since the recommendations from the advisory review panels were made, and the concerns about pediatric cough and cold products that have been presented to FDA, including those raised by the March 1, 2007, citizen petition, the agency has taken a new look at the assumptions that were used to create the pediatric conditions for cough and cold medicines contained in the CCABADP monograph. As part of this review, FDA convened a joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee on October 18 and 19, 2007, to discuss the safety and efficacy of these OTC cough and cold products marketed for pediatric use. The discussion at the Advisory Committee meeting addressed a variety of issues including the extrapolation of

efficacy data from adults to children of any age for cough and cold products; the safety profile of these products in children; the basis for dosing recommendations in the CCABADP monograph and the use of pharmacokinetic data to determine appropriate dosing in children; the basis of dosing recommendations for various age intervals of less than 2 years, 2 to 5 years of age, and 6 to 11 years of age; the use of the products in children less than 2 years of age; the potential for misuse, unintentional overdose, and excessive dosing; the ability of parents or caregivers to correctly dose and administer cough and cold products to their children; and the labeling changes recommended by the petitioner and the effects they would have on the use of these products in children and the recommendations of health care providers. The 22 person Advisory Committee was nearly unanimous in agreeing that new studies were necessary because extrapolation of efficacy data for the common cold indication from adults to children was not acceptable for children less than 2 years old or for children 2 years to less than 12 years. The vote was 22 to 0 and 21 to 1, respectively, for the two age groups. The committee understood that changing the OTC drug monographs required rulemaking that would take several years to complete. The Advisory Committee also voted 13 to 9 to recommend that pediatric cough and cold drugs should not be used for children under 6 years of age while rulemaking proceeded, and voted 15 to 7 to recommend that the products should continue, for the time being, to be sold for use in children ages 6 to under 12 while new studies are conducted.

On January 17, 2008, FDA issued a Public Health Advisory (PHA) available at: <http://www.fda.gov/cder/drug/advisory/cough_cold_2008.htm>. The PHA recommended that these drugs not be used to treat infants and children under 2 years of age because serious and potentially life-threatening side effects can occur. The PHA also indicated that FDA had not yet completed its review of the safety of these medicines in children 2 through 11, and the agency committed to completing the review as quickly as possible. Pending completion of this review, the PHA recommended a number of precautions for parents and caregivers using OTC cough and cold medicines in children 2 years of age and older, including carefully following the directions in the Drug Facts label; using appropriate measuring spoons or instruments made for measuring medicines; choosing products with safety caps; avoiding concurrent use of different OTC cough and cold medications to avoid unintentional overdose; not using these products to sedate children; and consulting a physician, pharmacist, or other health care professional with any questions about using these products in children.

In the PHA, we also announced strong support for the voluntary action taken by many pharmaceutical manufacturers to withdraw cough and cold medicines that were being sold for use in children under 2 years of age.

Since we issued the Public Health Advisory, we have continued our review of available data concerning the use of cough and cold medications in children, including information from the Advisory Committee meeting about the efficacy of the products, information from FDA's drug Adverse Event Reporting (AERS) database, and a published report in the medical literature from the Centers for Disease Control and Prevention (CDC) about children who ingested cough and cold medicines and had side effects that were serious enough to require an emergency room visit. While many of the observed adverse events were due to overdoses associated with accidental ingestions or dosing errors, allergic and non-allergic adverse events occurred with the labeled dose in children. FDA reviewed the CDC study and underlying data, particularly looking at the type of events that occurred with the labeled dose of OTC cough and cold medications, and noted that children under 4 years of age are more likely to experience non-

allergic adverse events than older children.

3Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse Events From Cough and Cold Medications in Children. *Pediatrics* 2008;121;783787; originally published online Jan 28, 2008.

Cough and cold products are commonly used in children. A recent report suggested that 1 in 10 children uses one or more cough and cold products during a given week with exposure being highest among 2 to 5 year olds, and high in children under 2.4<FTREF/> Based on the number of cases of serious adverse events reported to FDA and the number of serious adverse events in the CDC emergency room study, we believe that serious adverse events are relatively rare given the extensive use of the drug products.

4Boston University's Slone Epidemiology Center presentation at the 2008 Pediatric Academic Societies' & Asian Society for Pediatric Research Joint Meeting in Honolulu, Hawaii. Vernacchio L, Kelly JP, Kaufman DW, Mitchell AA. Cough and Cold Medication Use by US Children, 19992006: Results From the Slone Survey, *Pediatrics* 2008; 122:e323-e329.

Despite the fact that serious adverse events are relatively rare in children using cough and cold drugs, we have determined that the collection of additional data using modern standards is warranted to support the current dosing or to establish new dosing regimens for children, given the concerns that have been raised about the safety and efficacy of these products, particularly in younger age groups. Lack of safety and efficacy data for specific pediatric age groups also inhibits the conduct of a meaningful risk benefit analysis under 21 CFR 330.10(a)(4)(iii).

We recognize that many scientific issues must be addressed and resolved to support the development and review of data that, in the long term, will provide increased confidence in the safe and effective pediatric use of these OTC cough and cold products, either under the monograph or approved NDAs. FDA has decided to hold a Part 15 hearing to hear from the public, including parents, health care practitioners, manufacturers of cough and cold products, retailers, and other interested persons, about these issues. FDA will consider this public input in developing a proposed rule to amend the CCABADP monograph to reflect the new data and any appropriate changes to the conditions necessary to ensure that these medications can be considered GRAS/E.

II. Scope of Hearing

FDA is interested in obtaining public comment on the following issues relating to the use of pediatric cough and cold medicines:

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

2. Should cough and cold products for the pediatric population continue to be available OTC, or should they be made available only by prescription?
3. If the pediatric indications and dosing for cough and cold products were no longer available OTC, would the public use the adult formulations of the OTC monograph products for children, and thus create a greater risk of misuse or overdose?
4. Do the answers to the previous questions depend on the age of the pediatric patients? If so, how should age be considered in making regulatory decisions for these products?
5. At the time the monograph was established, FDA routinely extrapolated safety and efficacy data from adults to children age 12 and over. Current PREA standards permit extrapolation of pediatric efficacy -- but not safety-- based upon sufficient adult data. Does it remain appropriate to recommend in the cough and cold monograph that children 12 and over should receive the same dose of medication as adults, without requiring any additional studies in children in this age group? What additional safety and/or efficacy studies should be required in this age group?
6. What is the most appropriate method for determining pediatric doses that could be used as an alternative to the quarter- and half-dose assumptions used in the monograph? Should products be dosed by age, by weight, or both?
7. There are monographs for topical and intranasal ingredients to treat the common cold. Should these monographs be considered in a similar fashion to the oral cough and cold products? Are the answers to the previous questions different for any subcategories of cough and cold medicines (e.g., topical or intranasal products)?
8. The CCABADP monograph allows for the combination of ingredients to treat colds and/or coughs. Should combination products be permitted for all pediatric age groups? Should data be provided to support each unique combination?
9. Can measurement errors in dosing be reduced using more standardized measuring devices or alternative dosage forms and, if so, what is the best way to effect this change?

III. Notice of Hearing Under 21 CFR Part 15

The Commissioner is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, accompanied by FDA senior management from the Office of the Commissioner and the Center for Drug Evaluation and Research.

Under 15.30(f), the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation. Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10 (21 CFR part 10), subpart C)). Under 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in 15.30(b). To the extent that the conditions for the

hearing, as described in this document, conflict with any provisions set out in part 15, this document acts as a waiver of those provisions as specified in 21 CFR 15.30(h).

IV. Comments

Regardless of attendance at the public hearing, interested persons may submit written or electronic comments to the Division of Dockets Management (see ADDRESSES). Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments should be identified with the docket number found in brackets in the heading of this document. To ensure consideration, submit comments by (see DATES). Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Please note that on January 15, 2008, the FDA Division of Dockets Management Web site transitioned to the Federal Dockets Management System (FDMS). FDMS is a Government-wide, electronic docket management system. Electronic comments or submissions will be accepted by FDA through FDMS only.

V. Transcripts

Please be advised that as soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. It may be viewed at the Division of Dockets Management (see ADDRESSES). A transcript will also be available in either hard copy or on CDROM, after submission of a Freedom of Information request. Written requests are to be sent to Division of Freedom of Information (HFI35), Office of Management Programs, Food and Drug Administration, 5600 Fishers Lane, rm. 630, Rockville, MD 20857. Interested persons may submit to the Division of Dockets Management (see ADDRESSES) written or electronic notices of participation and comments for consideration.

Dated: August 20, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

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