FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee

October 18-19, 2007
Questions

The Agency has received a Citizen Petition requesting that FDA take action to re-label the OTC cough and cold products. The Petition states that these products are not safe or effective in children under the age of 6 years for treatment of cough and colds. The efficacy of the cough and cold ingredients was based on the extrapolation of efficacy from adults using a fraction of the adult dose. It should be noted that although the petitioners are requesting that the Agency take action on products for children less than 6 years of age, efficacy has also been extrapolated for children less than 12 years of age. Therefore, any actions recommended for children less than 6 may also apply to children less than 12 years of age.

The products regulated under the Final Monograph are considered to be Category I products, GRASE (generally recognized as safe and effective). If a decision is reached to require new studies for these products, rule making would be needed to re-categorize these ingredients to Category III (need more information) and sponsors would have the opportunity to perform these studies. If new studies are requested and do not establish efficacy or safety then products would be required to discontinue marketing.

1. Efficacy

a. Discuss the available published studies and how they inform our knowledge regarding the efficacy of the monograph cough/cold products in children.

b. Is it permissible to extrapolate data from adults to children or from older children to younger children for the cough and cold indications (yes/ no)? In answering, please consider whether the pathophysiology of the disease is similar in adults and children. If extrapolation is acceptable;

-please comment on when extrapolation would be appropriate.

-please comment on what additional PK studies should be conducted in order to better inform extrapolation for individual ingredients.

c. If extrapolation is not considered appropriate for cough/cold ingredients, please describe the data needed to demonstrate efficacy in children. For example, would clinical studies in children with clinical endpoints be necessary to support efficacy in children (yes/no)? If clinical trials are determined to be necessary, please comment on which ingredients and for which age groups

2. Safety

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 specifically address the safety of OTC cough and cold drug products for children under the age of 6 years when used in accordance with the labeled instructions and under a physicians care. Considering the widespread use of OTC cough and cold products

over decades, there are reported cases of serious adverse events. We are interested in understanding why these events happen and would like to be able to reduce the occurrence of preventable events.

a. Aside from the issue regarding excessive dosing, please comment on any significant safety issues that can be identified when these drugs are used at the currently recommended doses.

What additional safety data, if any, are needed to better understand the safety of these ingredients in children?

What actions do you recommend the agency consider in order to reduce the occurrence of adverse events related to factors associated with the drug (e.g., known toxicities) or the age group (e.g., variations in metabolism, variations in weight)?

b. Please comment on the contribution of mis-dosing to the overall safety profile of these products for each age group, and how this should affect their availability as OTC drug products.

c. Should dosing devices be required with liquid formulations (yes/no)?

Should all dosing devices (cups, spoons, syringes, etc.) bear only calibrations corresponding to, and identified with the same unit of measure, for the specific dosages described on the package labeling (yes/no)?

d. Please comment whether there are other formulations that will assist caregivers in providing the correct dose (for example, pre-measured drug).

3. Based on the discussions regarding efficacy and safety, are there age groups for which these ingredients should not be used right now (yes/no)? If so, which age groups and ingredients?

4. Labeling
Currently, the directions for some of the OTC cough and cold products such as the decongestants and antitussives, instruct a parent to "consult a doctor" for children under two years of age. The directions for OTC antihistamines instruct a parent to "consult a doctor" for children under 6 years of age. There is also 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 right for a child under their care. The labeling proposed in the petition would potentially limit the ability of physicians to prescribe OTC cough and cold products in children less than 6 years old and may also impact the labeling for children less than 12 years of age.

a. If there are age groups that should not use these products, discuss the language that should be used to convey this.

- The petitioner has recommended language: "These products have not been found to be safe and effective for 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". Do you agree with this wording (yes or no)?

- The Consumer Healthcare Products Association has recommended language for children less than 2 years of age: "Do not use". Do you agree with this wording (yes or no)? If these products are labeled with "Do not use" should this direction apply to consumers as well as to health care providers, such that no one will use these products?

- FDA regulations require the following labeling for antihistamines in children less than 6 years of age and all other ingredients in children less than 2 years of age: "Ask a doctor" or "Consult a doctor". Do you agree with this wording (yes or no)?

- Please discuss other labeling options we should consider.

b. We remind you that efficacy was also extrapolated for children less than 12 years of age. Should FDA consider similar labeling, as suggested by the petitioner for children less than 6 years of age, for children 6 - 11 years of age? Please respond yes or no. Discuss whether this would apply to all or only some ingredients.

c. If you decide that the use of some products in children less than 2 years old is <u>not</u> prohibited, please discuss how these products for children less than 2 years of age should be labeled.

d. Please discuss additional information that should be on the principal display panel to better inform consumers about the product.

e. Please discuss whether you believe the naming of the products contributes to consumer confusion.

5. Combination Products

Most cough and cold products are available as combination products. Combination products may be considered a problem because, for example, parents and caregivers may use several products not realizing that they are duplicating ingredients, and overdosing their children. Currently the monograph allows for combinations of several ingredients.

a. Should marketing of combination products be allowed for children (yes or no)? If no, for which age groups? In addressing this, please consider the following points:

- there may be advantages of combination products, assuming correct use
- there may be unintended consequences of prohibiting combination products in that parents will use multiple single ingredient products
- there may be disadvantages if overdosing occurs with multiple ingredients

If yes, should the number of active ingredients in combination products be limited in order to reduce the use of overlapping ingredients in different products (yes or no)?

b. Discuss whether labeling changes or other approaches can improve the safety of combination products. If so, what would you recommend? When answering this question, consider whether all indications for each ingredient should appear on the label.