**Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee**
**October 18-19, 2007**

This is the final report of the joint meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee held on October 18-19, 2007. A verbatim transcript will be available in about 2 weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder07.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information office.

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The Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration met on October 18-19, 2007 at the National Labor College, 10000 New Hampshire Ave., Silver Spring Maryland. Mary Tinetti M.D. and Marsha D. Rappley, M.D. chaired the meeting. There were approximately 400 in attendance.

**Attendance:**

**Nonprescription Drugs Advisory Committee Members present (voting):**
Mary E. Tinetti, M.D., Ernest B. Clyburn, M.D., Ruth M. Parker, M.D., Robert E. Taylor, M.D., Ph.D., F.A.C.P; Ralph B. D'Agostino, Ph.D., Marie R. Griffin, M.D., Jan L. Hewett, J.D., B.S.N., William H. Shrank, M.D., M.S.H.S.

**Nonprescription Drugs Advisory Committee Member absent :**
Garret A. FitzGerald, M.D.

**Pediatric Advisory Committee Members present (voting):**
Marsha D. Rappley, M.D., Dennis Bier, M.D., Avital Cnaan, Ph.D., M.S., Robert S. Daum, M.D., Leon Dure, M.D., Thomas Newman, M.D., M.P.H., Geoffrey L Rosenthal, M.D., Ph.D.,

**Pediatric Advisory Committee Members absent:**
Michael E. Fant, M.D., Ph.D., Melissa Maria Hudson, M.D., Keith Kocis, M.D., M.S., Robert Ward, M.D.

**Temporary Voting Members:**
Thomas P. Atkinson, M.D., Ph.D., William J. Calhoun, M.D., F.A.C.P., Amy J. Celento-Stamateris *(Patient/ Family Representative),* Michael R. Cohen, R.Ph., M.S., D.Sc., Sean P. Hennessy, Pharm.D., Ph.D., Jesse Joad, M.D., Richard A. Neill, M.D.

**Temporary Member (non-voting)**
Richard L. Gorman, M.D. *(Pediatric Health Organization Rep.)*

**Industry Representatives: (non-voting):**
George S. Goldstein, M.D. (NDAC), Elizabeth A. Garofalo, M.D (PAC).

**FDA Participants:**
John Jenkins, M.D., Charles Ganley, M.D., Joel Schiffenbauer, M.D., Robert Nelson, M.D., Ph.D., Ann W. McMahon, M.D., M.S.

**Open Public Hearing Speakers:**
Anthony R. Temple, M.D., F.A.A.P., David I. Bromberg, M.D., F.A.A.P., Winnie Landis, R.Ph., Patricia Jackson Allen, R.N., M.S., P.N.P., F.A.A.N., Peter Lurie, M.D., M.P.H., Daniel A. Mannello.

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On October 18-19, 2007, the committees met in joint session to discuss the safety and efficacy of over-the-counter (OTC) cough and cold products marketed for pediatric use.

On October 18th, Mary Tinetti, M.D., (NDAC Chair) and Marsha D. Rappley, M.D., (PAC Chair), called the meeting to order at 8:00 a.m. The Committee members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Darrell Lyons, BSN, Designated Federal Officer (DFO). The Agenda for the meeting was as follows:

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| 8:00 | Call to Order<br>Introduction of Committee | **Mary Tinetti, M.D.**<br>Chair, Nonprescription Drugs Advisory Committee |
| | | **Marsha D. Rappley, M.D.**<br>Chair, Pediatric Advisory Committee |
| | Conflict of Interest Statement | **Darrell Lyons, BSN, RN**<br>Designated Federal Official |
| 8:30 | OTC Cough and Cold Products:<br>Use in Children | **Joel Schiffenbauer, M.D., Deputy Director**<br>Office of Nonprescription Products CDER, FDA |
| 8:40 | Regulatory History of Pediatric Cough/Cold Products | **Marina Y. Chang, R.Ph., Team Leader**<br>Office of Nonprescription Products CDER, FDA |
| | **PETITIONER PRESENTATIONS** | |
| 8:55 | Cough and Cold Preparations for Young Children: Overview and Petition | **Joshua M. Sharfstein, M.D**.<br>Commissioner of Health, Baltimore City |
| | Efficacy of Cough and Cold Preparations for Young Children | **Wayne R. Snodgrass, M.D., Ph.D.**<br>Professor, University of Texas Medical Branch |
| | Safety of Cough and Cold Preparations in Young Children | **Michael Shannon, M.D., M.P.H.**<br>Professor of Pediatrics, Harvard Medical School |
| | Cough and Cold Preparations in Young Children: Practical Considerations | **Daniel J. Levy, M.D.**<br>President, MD Chapter, American Academy of Pediatrics |
| 10:00 | ***Break*** | |
| 10:15 | **INDUSTRY PRESENTATIONS** | |
| | Introduction | **Linda Suydam, D.P.A.**<br>President Consumer Healthcare Products Association |

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| | Efficacy Research | **Phil Walson, M.D.**<br>University of Cincinnati Pediatrician |
| | Pharmacokinetics | **Cathy Gelotte, Ph.D.**<br>McNeil Consumer Healthcare |
| | Safety | **Richard Dart, M.D.,**<br>Rocky Mountain Poison and Drug Center &<br>**Ed Kuffner, M.D.**<br>McNeil Consumer Healthcare |
| | Industry Commitments & Recommendations | **Linda Suydam, D.P.A.**<br>President, Consumer Healthcare Products Association |
| 12:00 | ***Lunch*** | |
| | **FDA PRESENTATIONS** | |
| 1:15 | Clinical Pharmacology Perspectives of Pediatric Dosing of OTC Cough & Cold Medicines | **Partha Roy, Ph.D., Senior Clinical Pharmacologist**<br>Office of Clinical Pharmacology CDER, FDA |
| 1:35 | Considerations for Extrapolation of Efficacy from Adults to Children; Examples and Experience from the Division of Pulmonary & Allergy Products | **Peter Starke, M.D., Associate Director for Safety & Charles E. Lee, M.D., Medical Team Leader**<br>Division of Pulmonary & Allergy Products CDER, FDA |
| 1:50 | Literature Review: Safety and Efficacy of OTC Cough/Cold Drug Products in Pediatric Patients | **Lolita A. Lopez, M.D., Medical Officer**<br>Office of Nonprescription Products CDER, FDA |
| 2:05 | Adverse Events and Poisonings Associated with Cough and Cold Products in Children Less Than 6 Years of Age | **Gita Akhavan-Toyserkani, Pharm.D., MBA, Safety Evaluator**<br>Office of Surveillance and Epidemiology,<br>CDER, FDA |
| 2:30 | Over-the-Counter Cough/Cold Products Medication Errors | **Richard Abate, R.Ph., M.S., Safety Evaluator**<br>Office of Surveillance and Epidemiology,<br>CDER, FDA |
| 2:45 | *Questions for Speakers* | |
| 3:15 | ***Break*** | |
| 3:45 | *Questions for Speakers/Committee Discussion* | |
| 5:00 | ***Adjourn*** | |

October 19, 2007

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| 8:00 | Call to Order<br>Introduction of Committee | **Mary Tinetti, M.D.**<br>Chair, Nonprescription Drugs Advisory Committee |
| | | **Marsha D. Rappley, M.D.**<br>Chair, Pediatric Advisory Committee *(via telephone)* |
| | Conflict of Interest Statement | **Darrell Lyons, BSN, RN**<br>Designated Federal Official |
| 8:30 | *Open Public Hearing* | |
| 10:30 | ***Break*** | |
| 10:45 | *Questions and Panel Discussion* | |
| 12:00 | ***Lunch*** | |
| 1:15 | *Questions and Panel Discussion* | |
| 4:00 | ***Adjourn*** | |

**Questions to the Committee:**

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 II (Not generally recognized as safe and effective) 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 for the common cold in children.

**Committee Discussion:**

*The committee felt that the published studies that were available did not demonstrate efficacy due to a number of reasons. The studies had limitations, they were few in number, the sample sizes were too small, and the studies were underpowered with inappropriate outcomes. The committee recommended more studies and data. (See Transcript for Complete Discussion)*

b. Is it appropriate 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.

**Committee Discussion:**
*For a point of clarification the committee defined and categorized children into two groups: (1) less than 2 years of age and (2) 2 years to less than 12 years of age; the committee further proposed changes in the wording of the question to:*

1. Is it appropriate to extrapolate data from adults to children, less than 2 years old, for the cough and cold indications in the common cold?
**Yes: 0** **No: 22** **Abstain: 0**

2. Is it appropriate to extrapolate data from adults to children, 2 years to less than 12 years old, for the cough and cold indications in the common cold?
**Yes: 1** **No: 21** **Abstain: 0**

3. Is it ever appropriate to extrapolate efficacy data within the childhood population, i.e., age 2 to less than 12 years of age, for the cough and cold indications in the common cold?
**Yes: 4** **No: 18** **Abstain: 0**

c. If extrapolation is not considered appropriate for cough/cold ingredients for common cold indications, 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.

*The committee proposed to change the wording of the question to:*
Would clinical studies, in children less than 12 years old, with clinical endpoints be necessary to support efficacy in children less than 12 years old?
**Yes: 22** **No: 0** **Abstain: 0**

**Committee Discussion:**
*The Committee agreed that clinical trials should focus on single ingredient studies with clear clinical endpoints that are pathophysiologically related to what the drug is expected to do, and that each ingredient should be studied one-by-one in children. The clinical endpoints used should include cough/cold symptoms, specifically, those for which the products are marketed for children. Sleep/sedation should not be an endpoint. Pharmacokinetic studies of single ingredients are also needed. (See Transcript for Complete Discussion).*

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.

**Committee Discussion:**
*The committee noted that the marketing of products with multiple ingredients and current product labeling is confusing; both lead to issues with the safe use of the products by the consumer. Also, the lack of standardization in dosing and, dosing devices, and dosing by age rather than by weight are significant safety concerns.*
*(See Transcript for Complete Discussion)*

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

**Committee Discussion:**
*The data suggest an increase in seizures, particularly in the 6-12 year old age group. The committee discussed the importance of determining whether these noted seizures represent adverse effects of the cold/cough medications or febrile seizures or other. Better estimates of the rates of adverse events of cough/cough medications are needed, although the committee recognized the difficulty in ascertaining these estimates. The committee recommended the following actions be taken: a further review of the existing safety data; the conduct of large, simple safety trials; the conduct of rigorous case control design and large post-market trials; and, surveillance that is more systematic than the current FDA postmarketing surveillance. The committee also*

*recommended standardization of dosing regimens, standardization of dosing devices, standardization of label wording, and standardized product units of measures. (See Transcript for Complete Discussion)*

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)? *(See Transcript for Complete Discussion)*

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.

**Committee Discussion:**
*The committee noted that according to the information in the FDA and Industry presentations, the highest chance for mis-dosing occurred when there was no dosing information available on the label. Therefore, the recommendation was for all products to list dosing instructions on the label for age groups for whom the medications are allowed. (See Transcript for Complete Discussion)*

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

**Committee Discussion:**
*The committee recommended standard wording for dosing, unit of measure, and concentration to reduce consumer errors and proposed changing the wording of the question to:*

Should dosing devices that are standardized in wording and dosing be required with liquid formulations?
**Yes: 22 No: 0 Abstain: 0**
*(See Transcript for Complete Discussion)*

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)?

**Committee Discussion:**
*There was no vote for this question as the committee addresses this issue in question 2c. (See Transcript for Complete Discussion)*

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

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?

**Committee Discussion:**
*The committee proposed the following question:*

a. Based on the discussions regarding efficacy and safety, should these ingredients (antihistamines, nasal decongestants, and antitussives) NOT be used now in children under the age of 2 for the common cold?
**Yes: 21 No: 1 Abstain: 0**

*Committee members also expressed concerns that the safety data presented, suggested significant differences in the 2 to 6 year old child population. Therefore, the committee recommended voting on whether they should recommend children age 2 and less than 6 years old not use these products now prior to voting on the age 6 to less than 12 child population.*
*(See Transcript for Complete Discussion)*

b. Should the committee recommend that these ingredients (antihistamines, nasal decongestants, and antitussives) NOT be used for the common cold right now for children between the ages of 2 and less than 6?
**Yes: 13 No: 9 Abstain: 0**

c. Should the committee recommend that these ingredients (antihistamines, nasal decongestants, and antitussives) NOT be used for the common cold right now for children between the ages of 6 and less than 12?
**Yes: 7 No: 15 Abstain: 0**

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.

**Committee Discussion:**
*The committee determined that the Petitioner's recommended language was too complicated and that requires simplification in order to allow ease of reading and understanding by the consumer. The committee recommended that standardized language and warnings, and universal symbols be developed and implemented after testing with consumers and patients. Overall, the committee did not agree with the Petitioner's recommended labeling language and therefore, a vote on the first bulleted question above was not taken. (See Transcript for Complete Discussion)*

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. *(See Transcript for Complete Discussion)*

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

Committee discussion: *The committee voted unanimously that these products should be prohibited in children less than two thus no labeling discussion took place. (See Transcript for Complete Discussion)*

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

**Committee Discussion:**
*Committee recommendations for labeling included:*
*1. Listing the ingredients, medication strength and concentration on the front label.*
*2. Removing "Doctor Recommended", and all similar statements, from the front panel.*
*3. Removing pictures of infants/babies/ and children from the box.*
*4. Listing patients that should NOT take the product*
*5. Stating that individuals should not simultaneously take more than one product with the same ingredient(s)*
*(See Transcript for Complete Discussion)*

e. Please discuss whether you believe the naming of the products contributes to consumer confusion.
*(See Transcript for Complete Discussion)*

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)?

**Committee Discussion:**
*The committee proposed changing the wording of the question:*

1. Assuming that these ingredients are proven safe and effective, should marketing for combination products be allowed for children between the ages of 2 to less than 6 years old for the common cold?

**Yes: 14** **No: 4** **Abstain: 3**

2. Assuming that these ingredients are proven safe and effective, should marketing for combination products be allowed for children between the ages of 6 to less than 12 years old for the common cold?

**Yes: 15** **No: 3** **Abstain: 3**

*(See Transcript for Complete Discussion)*

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.
**Committee Discussion:**
*The committee proposed changing the wording of the question:*

Should label comprehension and actual use studies be done prior to allowing marketing of combination products?

**Yes: 21** **No: 0** **Abstain: 0**

*The committee further recommended that all combination products contain a warning that states "Do not take with other cough/cold products." (See Transcript for Complete Discussion)*

The meeting was adjourned at approximately 4:00 p.m. on October 19, 2007.

These summary minutes for the October 18-19, 2007 Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration were approved on October 31, 2007.

I certify that I attended the October 18-19, 2007, Joint Meeting of the Nonprescription Drugs Advisory Committee and the Pediatric Advisory Committee of the Food and Drug Administration meeting and that these minutes accurately reflect what transpired.

_____/S/_____
Darrell Lyons, B.S.N
Designated Federal Officer

_____/S/_____
Mary Tinetti, M.D.
Chair, NDAC

_____/S/_____
Marsha D. Rappley, M.D.
Chair, PAC