MINUTES OF THE PEDIATRIC ADVISORY COMMITTEE

The public meeting was convened 8:30 a.m. to 4:00 p.m. on September 11, 2017

Advisory Committee Members Present	**Non-FDA Presenters**
Robert A. Dracker, MD, MHA, MBA – Acting Chair Jeffrey Brent, MD, PhD David Callahan, MD Jeffrey Campbell, MD, MS Mary Cataletto, MD Amy Celento, BS Melody Cunningham, MD Kort Delost, RPh Gwenyth Fischer, MD Peter Havens, MD, MS Sarah Hoehn, MD, MBe, FAAP Tamar Lasky, PhD Erica Liebelt, MD, FACMT James McGough, MD Steven Meisel, PharmD, CPPS Kathleen A. Neville, MD, MS Stephen W. Patrick, MD, MPH Jennifer Plumb, MD Wael Sayej, MD Kelly D. Stone, MD, PhD Christy Turer, MD, MHS, FAAP, FTOS Linda S. Tyler, PharmD Kelly C. Wade, MD, PhD Jeffrey S. Wagener, MD Michael White, MD, PhD, FACC, FAAP James McGough, MD Steven Meisel, PhD, CPPS Kathleen Neville, MD, MS, FAAP, FCCP Steven Patrick, MD, MPH, MS, FAAP Jennifer Plumb, MD, MPH, FAAP	John Oppenheimer, MD Leonard Lawrence Victor S. Sloan, MD, FACP, FACR Sharon Levy, MD, MPH
Non-Voting Members	**Designated Federal Official (DFO)**
Bridgette Jones, MD (*PHO Rep.)* Ronald Portman, MD (*Industry Rep.)* - phone	Marieann Brill, MBA, RAC, MT (ASCP)

U.S. Food and Drug Administration (FDA) Participants

Office of Pediatric Therapeutics Robert "Skip" Nelson, MD, PhD	**CDER Division of Pulmonary, Allergy, and Rheumatology Products** Peter Starke, MD, FAAP Sally Seymour, MD **CDER Division of Pediatric & Material Health** John Alexander, MD, MPH Amy Taylor, MD, MHS	**CDER Office of Surveillance and Epidemiology** Tracy Pham, PharmD Rajdeep Gill, PharmD Sara Karami, PhD, MPH Jacqueline Puigbo, PhD Grace Chai, PharmD Judy Staffa, PhD, RPh **CDER Office of the Center Director** Jason Bunting, PharmD

Welcome and Introductory Remarks

The meeting began at 8:30 am with Robert Dracker, the Acting Committee chair, welcoming everyone, and the participants introduced themselves.

- Marieann Brill, the Designated Federal Official, read the usual, customary, and required opening statements.
- John Alexander, MD, MPH gave opening remarks and provided an overview on the purpose of today's discussion for the PAC which focused on the benefit/risk profile in use of prescription opioid products (specifically, codeine and hydrocodone) for the treatment of cough. Over-the-counter (OTC) products are not the focus of today's meeting.

Taming Chronic Cough in the Peds World (Oppenheimer)

Dr. Oppenheimer's presentation focused on current treatment of cough in pediatric patients. Key points of the presentation are:

- Acute cough is a common cause of patient visits.
- Cough can be caused by local irritation (for example, mucosal irritation in the airways from upper respiratory tract inflammation due to acute upper respiratory tract infection [URI]) or by vagal stimulation.
    - Findings which may necessitate additional clinical investigations include the presence of lower respiratory tract signs, relentlessly progressive cough, hemoptysis or features of an undiagnosed chronic respiratory disorder.
- Since the common course of acute cough is usually spontaneous resolution within a couple of weeks, comprehensive clinical evaluation and symptomatic treatment of acute cough is not needed; however, when deemed necessary by a treating clinician, treatment should be directed toward the primary pathology rather than the symptom of cough.
- Over-the-counter (OTC) medications have little or no benefit in the treatment of acute cough in children, and medicines such as antihistamines, nasal decongestion combinations and other drug products are no more effective than placebo.

Background on the Use of Opioids as Antitussives

Dr. Starke provided an overview of prescription cough products and the labeling of these products for use in children. He provided a summary of the regulatory history of these products, including Drug Efficacy Study Implementation (DESI), Prescription (Rx) products, and Over-the-Counter (OTC) Monograph products. Key points included:

- Hydrocodone and codeine are the only opioids approved for treatment of cough. All are approved only as combination products. Hycodan, a hydrocodone product, is the only product approved by the FDA for the treatment of cough (not specifically related to the common cold or allergy). All the others are approved for the treatment of cough associated with the common cold or allergies.
- These and other opioid containing drugs readily cross the blood-brain barrier and all opioid/opiate products have on-target and off-target effects.
- Hydrocodone and codeine were originally approved when drug applications generally focused on adult data and when pre-market pediatric studies were not required for approval. After passage of the Kefauver Harris Amendment (1962), hydrocodone and codeine both underwent review for effectiveness under DESI provisions, were determined to be effective, and were listed as effective in a Federal Register.

Pediatric Outpatient Prescription Utilization of Opioid and Non-Opioid Containing Antitussives

Dr. Pham's presentation focused on national trends of prescriptions for opioid antitussives containing codeine and hydrocodone dispensed to children from U.S. outpatient retail pharmacies. National prescription dispensing trends of benzonatate and dextromethorphan (DXM), which are non-opioid containing antitussives, were also examined. Key points included:

- In 2016, about 5.8 million antitussive prescriptions were dispensed to pediatric patients 17 years of age and younger, representing a decrease since 2012. Among these, about 4.9 million prescriptions were dispensed for dextromethorphan containing antitussives in 2016, while about 471,000 prescriptions and 65,000 prescriptions were dispensed for codeine and hydrocodone containing antitussives, respectively.

Pediatric Cough & Cold Products: Analysis of American Association of Poison Control (AAPCC) Data, 2011-2016

Dr. Karami's presentation described an analysis of exposure calls to U.S. poison control centers for opioid-containing (hydrocodone and codeine) and non-opioid-containing (benzonatate and dextromethorphan (DXM)) cough and cold medications in children and adolescents under 18 years of age. Key points included:

From poison control center data, trends in annual rates for the underlying reason for which exposure occurred showed:

- From 2011 through 2016, the annual rate for adverse reaction calls decreased for DXM-containing antitussives from 3.9 to 2.7 per million population under 18 years of age, while the annual rates were lower and steady (less than 0.2 per million population) for benzonatate and opioid-containing antitussives.
- From 2011 through 2016, the annual rate for unintentional exposure calls increased for benzonatate from 8.5 to 15.8 per million population under 6 years of age, while the annual rates for DXM and opioid-containing antitussive calls decreased; the mean call rate per million population was 15.5 for codeine, 5.1 for hydrocodone, 11.6 for benzonatate, and 555.2 for DXM.
- From 2011 through 2016, the annual rate for intentional exposures calls decreased for DXM-containing antitussives from 113.9 to 84.3 per million population 12-17 years of age, while the annual rates were much lower for benzonatate and opioid-containing antitussives (less than 2.5 per million population).

Additional Considerations in the Use of Opioids for Cough

Dr. Taylor presented a summation on the principles of treatment of acute cough, treatment guidelines, global regulatory actions, current pediatric labeling, Pediatric Research Equity Act (PREA) requirements, and summary of an expert roundtable meeting held by FDA in preparation for this Advisory Committee meeting. Treatment of Acute cough in children is typically self-limited and commonly secondary to infection. The status of ongoing and planned required studies under PREA may be affected by the day's discussion.

Industry Presentation – Sovereign Pharmaceuticals

Mr. Lawrence of Sovereign Pharmaceuticals noted that the FDA has required an open label, single arm, single-dose PK study under PREA to assess their combination product containing guaifenesin and hydrocodone. Mr. Lawrence stated his company's position based on their assessment, is that the benefit/risk balance of studying opioid-containing products for treatment of cough in children younger than 12 years is not supported, the products should not be used in such children, and his company and other companies should be released from PREA requirements investigating such indications. In his experience, most Institutional Review Boards (IRB) would no longer allow these studies.

Industry Presentation – UCB Pharmaceuticals

Dr. Sloan noted that UCB reviews all its products on a regular basis, including routine pharmacovigilance and evaluation, by its internal benefit risk board. Upon annual review UCB determined that benefit risk balance for use of Tussionex for cough in children is no longer favorable. Key points included:

- Since approval there were 391 reports submitted to UCB. Of these reports, 35 described children less than 18 years of age with 13 reports of death, including 10 deaths in children under 6 years of age. Many of these were medication errors.
- As a result, UCB filed a labeling supplement to limit the use of their product to patients 18 years of age and older and maintain the contraindication in children below 6 years that is already in the Tussionex label.

Opioid Misuse and Opioid Use Disorders in Adolescents

Dr. Levy's presentation describes the effect of opiates and opioids on the adolescent brain and included a review of opiate/opioid metabolism. Key points included:

- While brain weights reach adult values by approximately 10 years, neurodevelopment including increased synaptic connections and pruning of synaptic connections continues into late adolescence/early adulthood.
- The amygdala, nucleus accumbens, and prefrontal cortex are related to developing understanding of reward, excitement, and decision making. Early exposure to opioids in childhood and adolescents permanently alters the anatomy and physiology of these brain and specifically the areas of reward perception, risk assessment, and decision making and likely enhance the likelihood of developing opiate/opioid misuse conditions and addictions compared to exposure compared to first ever exposure in adults.

Noon—13:00 Lunch

Open Public Hearing

Dr. Dracker began the open public hearing by reading the usual, customary, and required opening statement.

Public Comments

One comment was submitted to the docket prior to the meeting from the law firm of Hyman, Phelps, &

McNamara, P.C. Dr. Dracker informed the PAC that the comment was in the background package for review and comment by the AC members.

A second comment was presented by Dr. Dianne Zuckerman of the National Center for Health Research (NCHR). Dr. Zuckerman noted that a recent Cochrane review of codeine data in children ages 0 to 18 years reported that no data from randomized placebo-controlled trials supported the use of opioids for treatment of cough in children. Dr. Zuckerman concluded by stating that the benefit/risk profile for use of codeine identified risks including addiction and death, without evidence of benefit for the treatment of acute or chronic cough in children and adults.

PAC Question and Answer Period (Drs. Dracker & Alexander)
After the open public hearing was closed, the committee was given time to ask clarifying questions for the presenters.

Committee Discussion:
The committee questions are shown in bold text below:

Question 1 (Discussion): Discuss the benefit/risk of the use of prescription codeine and hydrocodone antitussives in pediatric patients in no particular order:

a. What are the benefits and risks for the codeine and hydrocodone products intended for treatment of cough associated with allergy or the common cold?

b. Does the benefit risk assessment change for treatment of cough in other specific circumstances?

c. Are there important differences in the benefit/risk between hydrocodone and codeine that would affect your recommendations about use in pediatric patients?

d. Are there differences in the benefit/risk assessment for specific pediatric age groups?

e. How do the wider public health concerns of opioid containing medications impact your benefit/risk assessment of codeine and hydrocodone products intended for treatment of cough?

- Several committee members stated the risk is both to individual patients based on patient specific adverse events, and risk to society for the risk of misuse, abuse, and addiction. Members noted a concern for access to these types of medications in the home and a need to decrease opioids in our communities.
- In terms of risk to individual patients, there were multiple comments that acute cough in children associated with the common cold and allergies is generally self-limited; these types of products are not standard of care and are antiquated.
- Members noted that the evidence for efficacy was limited, poor quality, or non-existent and would not be sufficient for today's standards. Several members acknowledged that opioids do work for cough, but the bigger issue was the overall lack of evidence of *benefit* for pediatric patients.
- Members also noted the lack of safety data, but indicated that any risk would not be acceptable if there is no benefit. There was discussion that codeine and hydrocodone have different risks. Codeine is higher risk because it is a high risk product related to CYPD6 polymorphism. Many hospitals have taken codeine off the formulary. For hydrocodone, there is insufficient information currently to quantify CYP2D6 or CYP3A4 polymorphism related risk.
- Several committee members stated that in rare circumstances codeine and hydrocodone could be

considered in pediatric patients, e.g. end of life, rib fracture, pertussis.

- The majority of members noted that the benefit/risk assessment is not favorable for the use of these products in children.
- Members also noted that codeine should not be allowed over the counter.
- To the extent possible, FDA should engage in professional and public education on the appropriate use (if any) of opioids for cough.

Question 2 (Voting): Is the benefit/risk favorable for use of prescription codeine cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients 12 to < 18 years of age? (Yes or No)

Vote tally: Yes: 0, No: 24, Abstain: 0

Comments included that there was no benefit; codeine was unpredictable; and given the self-limited nature of cough due to cold, the risk was unacceptable.

Question 3 (Voting): Is the benefit/risk favorable for use of hydrocodone cough suppressants for treatment of cough associated with allergy or the common cold in pediatric patients:

A. **6<12 years? Yes or No**

Vote tally: Yes: 1, No: 23, Abstain: 0

B. **12<18 years? Yes or No**

Vote tally: Yes: 1, No: 23, Abstain: 0

Comments included that there was no benefit and given the self-limited nature of cough due to cold, the risk was unacceptable. The person voting yes stated that hydrocodone is likely efficacious for treatment of acute cough; however, the characterization of real risk (not theoretical risk) for hydrocodone is not established as it is for codeine. This person also stated that while he believed that codeine did have a therapeutic effect on suppression of cough, he felt that the balance of risk outweighed the benefit for specific patients in the context of URI and allergy but that the risk to society appeared to be 'very low' due to his perception that there are few reports in the literature in spite of the number of years of use.

Question 4 (Voting): Is the benefit/risk favorable for use of prescription opioid cough suppressants for treatment of cough in pediatric patients? (Yes or No)

Vote tally: Yes: 2, No: 21, Abstain: 0

Comments included that the emphasis should be treatment of the underlying cause of the cough. The two persons voting “yes” stated the question was too broad such that a no vote would eliminate use for cough in 'rare' palliative situations or other scenarios of severe or refractory cough. Several members who voted no commented that the ability to use opioids/opiates for treatment of severe cough for non-URI/non-allergy scenarios should be rare and clinicians should continue to be able to prescribe opiates for cough off-label as a practice of medicine.

Adjournment: - Robert Dracker, MD, Acting Chair

FINAL APPROVAL:

/s/
Marieann R. Brill, MBA, RAC, MT(ASCP)
Designated Federal Officer, PAC

/s/
Robert Dracker, MD
Acting Chairperson, PAC