

MINUTES OF THE JOINT MEETING of the PEDIATRIC ADVISORY COMMITTEE (PAC) AND DRUG SAFETY AND RISK MANAGEMENT (DSaRM) ADVISORY COMMITTEE

The public meeting was convened from 1:00 p.m. to 2:00 p.m. September 26, 2019

<p><u>Members Present (voting)</u> Kelly Wade, MD, PhD (<i>Chair</i>) Premchand Anne, MD, MBA, MPH, FACC David Callahan, MD Randall Flick, MD, MPH Peter Havens, MD, MS Sarah Hoehn, MD, MBe, FAAP Randi Oster, MBA Wael Sayej, MD Christy Turer, MD, MHS, FAAP, FTOS Benjamin Wilfond, MD Sonia Hernandez-Diaz, MD, MPH, DrPH Marie R. Griffin, MD, MPH Laurel A. Habel, MPH, PhD Martin Kulldorff, PhD Steven B. Meisel, PharmD, CPPS Suzanne B. Robotti</p>	<p><u>Temporary Voting Members</u> Amy Celento, BS Angela Czaja, MD, MSc Richard Holubkov, PhD Timothy Lesar, PharmD James McGough, MD Roberto Ortiz-Aguayo, MD, MMM Stephen Patrick, MD, MPH, MS Jeanmarie Perrone, MD Lynn Sleeper, ScD Terri Voepel-Lewis, RN, PhD</p> <p><u>Non-Voting Members</u> Bridgette Jones, MD, MS Ronald Portman, MD, FAAP</p> <p><u>Designated Federal Officer (DFO)</u> Marieann Brill, MBA, RAC, MT(ASCP)</p>
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U.S. Food and Drug Administration (FDA participants)

<p>Office of Pediatric Therapeutics Susan McCune, MD</p> <p>CDER Division of Pediatric & Material Health Ethan D. Hausman, MD</p>	<p>CDER Office of Surveillance and Epidemiology Judy Staffa, PhD, RPh Radjeep Gill, PharmD Jana McAninch, MD, MPH, MS Chaitali Patel, PharmD, BCPS Ibrahim T. Ibrahim, PharmD, MPH, BCPS Christina R. Greene, PhD Daniel Bak, PharmD</p>	<p>CDER Division of Anesthesia, Analgesia, and Addiction Products Ellen Fields, MD, MPH Joshua Lloyd, MD</p>
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Welcome and Introductory Remarks

- Kelly Wade, Chair, Pediatric Advisory Committee (PAC) opened the meeting. Dr Wade directed those participating in the meeting and the audience to press representative Sandy Walsh, Press Officer, OC/OEA/OMA.
- Marieann Brill, Designated Federal Officer (DFO), read the usual, customary, and required disclosures and conflict of interest statement.
- Susan McCune, MD, Director of the Office of Pediatric Therapeutics gave opening remarks
 - Dr. McCune announced the topics for discussion for the September 26th and 27th joint PAC and Drug Safety and Risk Management (DSaRM) Committee meetings
 - Dr. McCune provided an update on the:

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- Web-posted pediatric-focused safety reviews available at <https://www.fda.gov/advisory-committees/pediatric-advisory-committee/web-posted-pediatric-safety-reviews>
 - 4 CBER products
 - 22 CDER products
 - 5 CDRH products
 - The docket was opened for comments until October 7, 2019.
- Non-compliance letters
 - 2 CBER non-compliance letters (none new since the April 2019 PAC Meeting)
 - 31 CDER noncompliance meeting (none new since the April 2019 PAC meeting)

American Academy of Pediatrics (AAP) Presentation on Use of Opioid Products in Pediatrics

- Jennifer Foster, MD, MPH, Department of Pediatrics, Baylor College of Medicine, AAP, Member, Committee on Drugs – “Prescription Opioids in Children: Importance of Accurate Labeling and Treatment of Pain”
 - Dr. Foster discussed the need to balance the goal of stopping opioid misuse and preventing and treating opioid addiction with the goal of treating severe pain effectively and safely in children who require pain management. Dr Foster summarized policy considerations for achieving the balance of the goals and shared some of the AAP’s policy initiatives. Dr. Foster also discussed pediatric opioid drug studies and labeling.

Discussion of the Pediatric-Focused Safety Review for Oxycontin (oxycodone hydrochloride) Extended-Release Tablets and Pediatric Data Considerations for Opioid Analgesics Labeling and PREA Studies for Opioids Generally, Using Opana IR as an Example

- Joshua Lloyd, MD, Clinical Team Leader, Division of Analgesia, Anesthesia, and Addiction Products (DAAAP), ODE II, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER) – “Pediatric Pain and the Approach to Studying Opioid Analgesics in the Pediatric Population”
 - Dr. Lloyd described (i) the pediatric drug legislation; (ii) DAAAP’s approach for studying analgesics (specifically opioids) in the pediatric population; and (iii) the recently approved pediatric labeling for Oxycontin.
- Ibrahim T. Ibrahim, PharmD, MPH, BCPS, Drug Utilization Analyst, Division of Epidemiology (DEPI)-II, Office of Surveillance and Epidemiology (OSE), CDER – “Pediatric Utilization Patterns of Opioid Analgesics”
 - Dr. Ibrahim summarized the pediatric utilization patterns of opioid analgesics between 2009-2019, including the (i) national sales distribution data; (ii) the outpatient retail pharmacy utilization data (including the prescription and patient-level data and the top prescriber specialties); and (iii) office-based physician surveys. Dr. Ibrahim also described the limitations of the utilization data.
- Christina R. Greene, PhD, Epidemiologist, Drug Abuse Team II, DEPI-II, OSE, CDER – “Prescription Opioid Abuse and Related Outcomes in the Pediatric Population”
 - Dr. Greene summarized the available epidemiologic data to inform considerations of risk related to pediatric opioid use. Dr. Greene (i) defined misuse and abuse; summarized the descriptive epidemiology of pediatric opioid misuse/abuse; and described the literature on

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risk of misuse/abuse and substance use disorders following pediatric prescription opioid therapy. Dr. Greene also discussed the limitations of the findings.

Open Public Hearing

- Two speakers: (see meeting transcript).

Presentation of Oxycontin Safety Reviews

- Daniel Bak, PharmD, Drug Utilization Data Analyst, DEPI II, OSE, CDER – “Pediatric Utilization Patterns of Single-Ingredient Oxycodone (Extended-Release and Immediate Release), 2013-2018”
 - Dr. Bak provided a general overview of the outpatient use of single-ingredient oxycodone IR and ER and the pediatric utilization of both products in the outpatient retail setting. Dr. Bak also summarized the findings on top prescriber specialties and diagnoses associated with the use of single-ingredient oxycodone. Dr. Bak discussed the limitations of the findings.
- Chaitali Patel, PharmD, BCPS, Safety Evaluator, Division of Pharmacovigilance (DPV)-II, OSE, CDER – “Pediatric Focused Safety Review: Oxycontin (Oxycodone hydrochloride Extended-Release)”
 - Dr. Patel summarized FDA’s analysis of the pediatric-focused safety review of Oxycontin (oxycodone hydrochloride ER).

Pediatric Data Considerations for Opioid Analgesics Labeling and PREA Studies for Opioids Generally, Using Opana IR as an Example

- Joshua Lloyd, MD, Clinical Team Leader, DAAAP, ODE II, OND, CDER – “Opioid Analgesics: Translating Pediatric Study Results into Labeling”
 - Dr. Lloyd summarized the required studies that are conducted under PREA for an immediate release opioid using OPANA (oxymorphone IR) as an example.

Committee Vote and Discussion

Dr. McCune clarified the background information that was presented was to inform the separate discussions of the OxyContin pediatric-focused safety review (under the Best Pharmaceuticals for Children Act [BPCA]) and the Opana pediatric labeling question (under PREA, pediatric studies were required). In terms of the pediatric-focused safety review of Oxycontin, committee members asked clarifying questions about what could be done besides routine safety monitoring and commented that the decreased prescribing and few adverse events reported are reassuring.

Dr. Hausman clarified what is meant by ongoing routine, post-market safety monitoring and clarified that it involves an active process.

1. **VOTE:** No new safety signals were identified for Oxycontin (oxycodone hydrochloride) extended-release tablets in the current pediatric safety review. FDA recommends continuing ongoing, routine, post-market safety monitoring, along with completion of the post-marketing required studies by the sponsor. Does the Committee agree?

Vote Results:

Yes: 20

No: 5

Abstain: 0

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Committee Discussion: The committee members who voted “no” expressed the need for rigorous studies, long-term safety studies, and the need for REMS or other controls on prescribing.

2. **DISCUSSION:** Pediatric patients have a need for adequate pain management that includes the use of opioids when appropriate. To accomplish this, product labeling should include appropriate pharmacokinetic, safety, and dosing information from clinical studies. Discuss appropriate strategies for describing the results of studies conducted under PREA in labeling taking into consideration the public health considerations of opioid misuse and abuse.
3. **DISCUSSION:** Extrapolation of efficacy from adults to pediatric populations down to two years of age and older for opioid analgesics has been acceptable provided that pharmacokinetic (PK) data demonstrate similar systemic exposure for adults and the pediatric population, and there are no additional safety concerns based on studies of pediatric patients with pain. However, situations arise in which the PK data demonstrate comparable exposures to the drug, but available efficacy data from the open-label safety study suggest dosing may not have been sufficient to provide adequate efficacy in the pediatric population as suggested in the study of Opana IR. Discuss whether information from the study in pediatric patients should be included in labeling, and if so, what information to include.
4. **DISCUSSION:** In the studies of Opana IR, notably higher systemic exposures were observed in 2 of the 24 patients in the PK and safety study conducted in 12 to 17 years of age (although one set of values suggests possible contamination of the sample). The patients did not experience any serious safety issues associated with these high levels. Discuss the implications of a small number of patients with higher than expected drug levels when considering labeling an opioid analgesic with information from pediatric studies.

Committee Discussion (for Discussions #2 – 4): The committee members discussed the issue of including PK and other information in drug labeling if the drug is not indicated for children. Committee members also emphasized the need for labeling information due to off-label use.

There were differing opinions about the proposed Opana labeling – one was that the proposed labeling gives a false sense of safety and that “safety and efficacy have not been established” is appropriate. The other opinion was that if FDA has pediatric data, those data should go into the labeling, so that providers can know what effectiveness and safety data exist, and decide what to do, again emphasizing that off-label use will occur regardless of labeling. Overall, committee members thought providers and parents need more information.

One committee member expressed concerns that the Sponsor wants to have pediatric information in the labeling without providing an indication so they can sell the product without liability. He also commented that clinicians do not rely on FDA labeling, but go to other sources like Micromedex for information. Other committee members expressed concerns about the available data for Opana including the small sample size, the number of withdrawals for lack of efficacy, and the validity of extrapolation of efficacy for pain treatment.

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5. **VOTE:** Should pediatric labeling be approved for Opana IR (immediate-release oxymorphone)?
a. If so, how should the pediatric information be described in labeling?

Vote Results: **Yes: 8** **No: 16** **Abstain: 1**

Committee Discussion: Committee members who voted “yes” verbalized generally that they believed some information is better than no information, and the data in labeling would need to be qualified and well-described. Committee members who voted no had concerns that there would be a false sense of safety and implied endorsement based on the results of the studies with such a limited number of patients and they were worried about lack of efficacy and possible harm if results of this limited nature were relied upon by clinicians.

Adjournment

- Kelly Wade, Chair, PAC

The summary minutes for the September 26, 2019 joint meeting of the PAC and DSaRM Advisory Committee were approved on October 30, 2019.

I certify that I attended the September 26, 2019 joint meeting of the PAC and DSaRM Advisory Committee and that these minutes accurately reflect what transpired.

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

_____/s/_____
Kelly Wade, MD
Chair, PAC