Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
November 15, 2018

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committee discussed the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. The committee were also asked to comment on the trial design and endpoints of these studies and how to determine the clinical relevance of the results.

These summary minutes for the November 15, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration were approved on December 18, 2018.

I certify that I attended the November 15, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Brian Bateman, MD, MSc
Designated Federal Officer, AADPAC	Acting Chairperson, AADPAC

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
November 15, 2018

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 15, 2018, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA. The meeting was called to order by Brian Bateman, MD, MSc (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 75 people in attendance. There were two Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. The committee were also asked to comment on the trial design and endpoints of these studies and how to determine the clinical relevance of the results.

Attendance:
Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Brian T. Bateman, MD, MSc (Acting Chairperson); Basavana G. Goudra, MD, FRCA, FCARSCI; Ronald S. Litman, DO, ML; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Raeford E. Brown, Jr., MD, FAAP; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; Lonnie Zeltzer, MD

Temporary Members (Voting): Daniel Budnitz, MD, MPH; James S. Floyd, MD, MS; Jennifer Higgins, PhD (Acting Consumer Representative); Karl Lorenz, MD, MSHS; Edward Michna, MD, JD, RPh; Joseph O'Brien, MBA (Patient Representative); Jack M. Rosenberg, MD; Maria E. Suarez-Almazor, MD, PhD

FDA Participants (Non-Voting): Patrizia Cavazzoni, MD; Peter P. Stein, MD; Sharon Hertz, MD; Pamela Horn, MD; Judy Staffa, PhD, RPh

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers: Neil Singla, MD; Ashley Walton (American Society of Anesthesiologists)

The agenda was as follows:

Call to Order and Introduction of Committee	**Brian Bateman, MD** Acting Chairperson, AADPAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, AADPAC
FDA Opening Remarks	**Sharon Hertz, MD** Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE-II) Office of New Drugs (OND), CDER, FDA
INDUSTRY PRESENTATIONS	**Biotechnology Innovation Organization (BIO)**
Methodologies for Determining Opioid Sparing in Acute Pain Models	**Richard Scranton, MD, MPH** Chief Medical Officer Head Medical Health Sciences Pacira Pharmaceuticals
Outcome Measures: A Composite Approach for Opioid Sparing Treatments in Chronic Pain	**Randall Stevens, MD** Chief Medical Officer Centrexion Therapeutics
Opioid Sparing Considerations in Chronic Pain Trials: Osteoarthritis as a Model Indication	**Scott Kelley, MD** Chief Medical Officer Flexion Therapeutics, Inc.
Clarifying Questions	
GUEST SPEAKER PRESENTATION	
The Role of Acute Care Prescribing in the Opioid Epidemic	**Chad M. Brummett, MD** Associate Professor Co-Director, Michigan Opioid Prescribing Engagement Network (Michigan OPEN) Director, Pain Research Department of Anesthesiology Division of Pain Medicine Michigan Medicine University of Michigan
Clarifying Questions	
BREAK	

GUEST SPEAKER PRESENTATION

How Risky is Opioid Pain Management During Adolescence? Persistent Use, Misuse and Abuse	**Terri Voepel-Lewis, PhD, RN** Associate Professor, School of Nursing Adj. Associate Research Scientist Department of Anesthesiology C.S. Mott Children's Hospital University of Michigan
Clarifying Questions	

FDA PRESENTATIONS

Background and Rationale for the Development of Opioid-Sparing and Opioid-Replacement Drugs	**Mallika Mundkur, MD, MPH** Clinical Reviewer Division of Pharmacovigilance II (DPV-II) Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology CDER, FDA
Study Designs and Approved Product Labeling Relevant to Opioid Sparing	**Pamela Horn, MD** Clinical Team Leader DAAAP, ODE-II, OND, CDER, FDA
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Sharon Hertz, MD**
Questions to the Committee/ Committee Discussion	

BREAK

Questions to the Committee/ Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION**: Discuss how to define a clinically meaningful decrease in opioid use to support an opioid-sparing claim, considering the following options:

    a. Statistically significant difference in average opioid use, considering that minor differences in opioid use could reach statistical significance but may not be clinically-relevant and, conversely, that there could be a clinically-relevant decrease in opioid exposure for many patients that is not reflected by a substantial difference in mean opioid use between groups
    b. A reduction by an absolute amount (in morphine milligram equivalents, for example) or percentage decrease in opioid use
    c. A decrease in the duration of opioid analgesic therapy that is required in the inpatient setting, for example, opioid analgesics only being required for the immediate postoperative period (i.e., the day or night of the procedure)

    Committee Discussion*: The committee members acknowledged the need to reduce opioid use and abuse. However, they expressed concern in labeling a medication as having 'opioid sparing' effects and agreed that the term needs to be more clearly defined to be specific to the type of surgery while taking into account patient specific characteristics. Some committee members expressed concern that labeling medications in a broad manner as being 'opioid sparing' may have unintended consequences such as overuse of medication, inappropriate prescribing and lack of efficacy in patients. One committee member added that introducing such labeling may lead to perverse incentives in clinical trials and drug development where the standard approach to treating analgesia may be withheld in ways that may not reflect real world practice, which could result in exaggeration of the effect of 'opioid sparing' medications. Overall, the committee members agreed that statistically significant difference alone has no significance as it is unknown how the results translate to clinical outcomes. In regard to reducing an absolute amount or percentage decrease in opioid use, some committee members noted that quantified reductions in opioid prescribing may be difficult to achieve due to individual patient specific factors and challenges in how it could be achieved in real world practice. Some committee members agreed that a decrease in the duration of opioid analgesic therapy could be impactful, but again noted that it would be dependent on the clinical circumstances on patients being treated. Please see the transcript for details of the Committee discussion.*

    d. The number of patients who use no opioid in the hospital, even if they are prescribed opioids at discharge for use at home
    e. The number of patients who do not require opioid analgesics after discharge, regardless of analgesic regimen while hospitalized

    Committee Discussion*: One committee member stated that the number of patients who used no opioid in the hospital, even if they are prescribed opioids at discharge, is not clinically meaningful as follow-up and evaluating this metric would be difficult. This committee member added that most patients will need opioids early on, but for a majority*

of situations, this would not be a primary outcome. Another committee member added that the opioid sparing approach in the hospital does not translate into sustained benefit after discharge. In regard to the number of patients who do not require opioid analgesics after discharge, regardless of analgesic regimen while hospitalized, committee members agreed that this would be a meaningful outcome. One committee member added that a Phase IV study using an active comparator within current standards of care with this outcome would define a clinically meaningful decrease in opioid use to support an opioid-sparing claim. Please see the transcript for details of the Committee discussion.

f. A reduction in opioid-related adverse reactions, e.g., nausea, vomiting, constipation, respiratory depression, sedation, urinary retention
g. Other criteria for defining a clinically-meaningful decrease in opioid use

***Committee Discussion**: The majority of the committee agreed that a reduction in opioid-related adverse reactions does not demonstrate a clinically meaningful decrease in opioid use to support an opioid-sparing claim as it would be difficult to correlate adverse events with opioid sparing since they are not directly analogous. The committee members agreed that other criteria that may be clinically meaningful include: measuring persistent opioid use beyond a defined time point, time to mobilization, time to meet surgery specific functional goals, and integrated global measures of pain management and recovery from surgery. Please see the transcript for details of the Committee discussion.*

2. **DISCUSSION**: Discuss the pros and cons of the following study designs to assess opioid-sparing or, alternatively, a novel design to assess opioid-sparing:

   a. study drug vs. placebo with opioid restricted to rescue
   b. standard of care with add-on of study drug or placebo

   ***Committee Discussion**: This question was skipped based on the Committee's discussion in Question #1.*

3. **DISCUSSION**: Discuss how much difference in analgesia (if any) would be permissible in a study of an opioid-sparing drug, relative to the standard of care with an opioid.

   ***Committee Discussion**: The committee agreed that a difference in analgesia would not be permissible in a study of an opioid-sparing drug relative to the standard of care with an opioid. Some committee members agreed that the difference in analgesia would be best measured not only at the pain intensity level, but with more global measures including functional measures although they're not clearly defined. Please see the transcript for details of the Committee discussion.*

4. **DISCUSSION**: Discuss the study design for a study of a novel non-opioid analgesic intended to be used in place of an opioid analgesic taking the following points into consideration:

a. Discuss whether any evidence of efficacy is enough when evaluating a novel analgesic intended to replace an opioid, i.e., whether adequate analgesia is an acceptable outcome
b. Discuss when the use of an active comparator is necessary to make a determination that a novel analgesic provides "opioid-level" analgesia in a setting usually managed with an opioid analgesic
c. Discuss how the use of rescue medication should be taken into account in the evaluation of efficacy in this setting

***Committee Discussion**: The majority of the committee members expressed that a study design for a novel non-opioid analgesic intended to replace an opioid should evaluate the difference in efficacy between the novel analgesic and existing opioids as they are the standard of care. The committee members also agreed that a trial that is attempting to prove that a novel non-opioid analgesic provides "opioid-level" analgesia would likely require an active comparator design where opioids may be used as rescue therapy. One committee member expressed the need for extensive toxicity data of the novel non-opioid analgesic prior to it being introduced to the market as it would likely affect millions of patients. Please see the transcript for details of the Committee discussion.*

5. **VOTE**: Is any reduction in opioid use sufficient to warrant labeling as opioid sparing?

   a. If not, describe the criteria that would support such labeling.

Vote Result: Yes: 1 No: 11 Abstain: 1

***Committee Discussion**: The majority of the committee members voted "No", that any reduction in opioid use is not sufficient to warrant labeling as opioid sparing. These committee members agreed that there is no evidence to support a broad labeling such as opioid sparing and added that reductions in opioid use should be more specific to patient/care settings for it to be meaningful. The one committee member who voted "Yes" stated that it is possible for a new drug that is shown to be equally efficacious to opioids with fewer incidences of adverse events to be labeled as opioid sparing in certain conditions. The one committee member who abstained from voting explained that the notion of opioid sparing is incorrect. Please see the transcript for details of the Committee discussion.*

6. **VOTE**: Is it sufficient to claim opioid-level analgesia for a novel analgesic based on the clinical trial population and without an opioid active comparator?

   If not, describe the type of comparisons that would provide support for a finding of opioid-level analgesia

Vote Result: Yes: 1 No: 12 Abstain: 0

***Committee Discussion**: The majority of the committee members voted "No", that it is not sufficient to claim opioid-level analgesia for a novel analgesic based on the clinical trial population and without an opioid active comparator. These committee members agreed that any new treatment should be compared to opioids since they are the standard of care. One committee member stated that a robust study would be required to determine equivalence based on outcome comparisons. The one committee member who voted "No" stated that opioid-level analgesia could be defined depending on the particular subgroup or specific surgical procedure. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 4:09 p.m.