

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee,
the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory
Committee Joint Meeting
September 15-16, 2016**

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

Topic: The purpose of this public advisory committee meeting was to discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation.

These summary minutes for the September 15-16, 2016, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee of the Food and Drug Administration were approved on October 11, 2016.

I certify that I attended the September 15-16, 2016, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/s/
Stephanie L. Begansky, PharmD
Designated Federal Officer, AADPAC

_____/s/
Raeford Brown, MD
Chairperson, AADPAC

**Summary Minutes of the
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the
Drug Safety and Risk Management Advisory Committee and the Pediatric Advisory
Committee
September 15-16, 2016**

The following is the final report of the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee held on September 15-16, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Analgesia, Anesthesia and Addiction Products, the Office of Safety and Epidemiology, and the Office of Pediatric Therapeutics and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm> and,
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm> and,
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm486581.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee of the Food and Drug Administration, met on September 15-16, 2016, at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503), 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 Raeford E. Brown, Jr., MD, FAAP (Chairperson). The conflict of interest statement was read into the record by Stephanie Begansky, PharmD (Designated Federal Officer). There were approximately 100 people in attendance each meeting day. There were 4 Open Public Hearing (OPH) speaker presentations.

Issue: The purpose of this public advisory committee meeting was to discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):
Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP (Chairperson); David S. Craig, PharmD; Charles W. Emala Sr., MS, MD; Anita Gupta, DO, PharmD (via telephone on day 1); Jennifer G. Higgins, PhD (Consumer Representative); Alan D. Kaye, MD, PhD; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD

September 15-16, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Jeffrey L. Galinkin, MD, FAAP; Rafael V. Miguel, MD

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

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Tobias Gerhard, PhD, RPh; Linda Tyler, PharmD, FASHP (via telephone)

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Christopher H. Schmid, PhD; Andy S. Stergachis, PhD, RPh; Til Sturmer, MD, MPH, PhD; Almut G. Winterstein, RPh, PhD, FISPE (Chairperson)

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting): Linda Scarazzini, MD, RPh (Industry Representative)

Pediatric Advisory Committee Members Present (Voting): Mary Cataletto, MD, FAAP; Avital Cnaan, PhD; Robert Dracker, MD, MBA, MHA; Peter Havens, MD, MS; Sarah Hoehn, MD, MBe, FAAP; Mark Hudak, MD; Christy Turer, MD, MHS, FAAP, FTOS; Kelly Wade, MD, PhD; Michael White, MD, PhD

Pediatric Advisory Committee Members Not Present (Voting): Melody Cunningham, MD; Erin Moore, BS (Patient-Family Representative)

Pediatric Advisory Committee Members Present (Non-Voting): Bridgette Jones, MD (Pediatric Health Organization Representative); Samuel D. Maldonado, MD, MPH, FAAP

Temporary Members (Voting): Sean P. Alexander, MD (Day 1 only); Stephanie Crawford, PhD, MPH; Angela S. Czaja, MD, MSc; Randall P. Flick, MD, MPH; Arthur F. Harralson, PharmD, BCPS; Arthur H. Kibbe, PhD; Tamar Lasky, PhD, FISPE; Lynne G. Maxwell, MD; Melanie Dawn Nelson, PhD (Patient Representative); Kathleen A. Neville, MD, MS, MBA; Stephen W. Patrick, MD, MPH, MS; Anne-Michelle Ruha, MD; Gary A. Walco, PhD

FDA Participants (Non-Voting): Sharon Hertz, MD; Ellen Fields, MD; Judy Staffa, PhD, RPh; Robert "Skip" Nelson, MD, PhD; Lynne Yao, MD; LCDR Grace Chai, PharmD

Designated Federal Officer (Non-Voting): Stephanie Begansky, PharmD

Open Public Hearing Speakers: Shoba Malviya (American Society of Anesthesiologists); Edwin R. Thompson (Pharmaceutical Manufacturing Research Services, Inc.); Stacy Baldrige (Purdue Pharma); Constance Houck (American Academy of Pediatrics)

September 15-16, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee

The agenda was as follows:

Day 1: Thursday, September 15, 2016

Call to Order and Introduction of Committees

Raeferd E. Brown Jr., MD, FAAP
Chairperson, AADPAC

Conflict of Interest Statement

Stephanie L. Begansky, PharmD
Designated Federal Officer, AADPAC

FDA Introductory 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

**AMERICAN ACADEMY OF PEDIATRICS
PRESENTATION**

Prescription Opioids in Children - Towards a Safer and Pain-free Tomorrow

Rohit Sheno, MD, FAAP
Associate Professor of Pediatrics
Baylor College of Medicine
Attending Physician, Emergency Center
Texas Children's Hospital, Houston

FDA PRESENTATIONS

Pediatric Drug Development Regulatory Considerations

Lynne Yao, MD
Director
Division of Pediatric and Maternal Health
Office of Drug Evaluation IV (ODE-IV)
OND, CDER, FDA

Additional Safeguards for Children in Clinical Investigations (21 CFR 50, Subpart D)

Robert "Skip" Nelson, MD, PhD
Deputy Director and Senior Pediatric Ethicist
Office of Pediatric Therapeutics (OPT)
Office of Special Medical Programs (OSMP)
Office of the Commissioner, FDA

Pediatric Utilization of Opioid Analgesic Products

Tracy Minh Pham, PharmD
Drug Utilization Analyst
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Clarifying Questions

September 15-16, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee

BREAK

FDA PRESENTATIONS (CONT.)

Current Approach to Studying Opioid Analgesics in Pediatric Patients

Steven Galati, MD
Medical Reviewer
DAAAP, ODE-II, OND, CDER, FDA

Clinical Pharmacology Considerations for Pediatric Studies of Opioid Drug Products

Srikanth C. Nallani, PhD
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 2
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS), CDER, FDA

Clarifying Questions

LUNCH

GUEST SPEAKER PRESENTATION

Pharmacotherapy for Pediatric Acute Pain, Chronic Pain, and Palliative Care

Charles Berde, MD, PhD
Sara Page Mayo Chair and Chief, Division of Pain Medicine, Department of Anesthesiology, Perioperative and Pain Medicine
Boston Children's Hospital
Professor of Anaesthesia (Pediatrics)
Harvard Medical School

PEDIATRIC ORTHOPAEDIC SOCIETY OF NORTH AMERICA PRESENTATION

The Use of Opioid Narcotics for the Pediatric Orthopaedic Patient

Harold J. P. van Bosse, MD
Associate Professor of Orthopaedic Surgery
Temple University, Philadelphia
Attending Pediatric Orthopaedic Surgeon
Shriners Hospital for Children, Philadelphia

Clarifying Questions

BREAK

GUEST SPEAKER PRESENTATIONS

Ethical Framework for Considering Pediatric Opioid Policy

Chris Feudtner, MD, PhD, MPH
Director, Department of Medical Ethics
The Children's Hospital of Philadelphia
Professor of Pediatrics, Medical Ethics and Health Policy
The Perelman School of Medicine at the University of Pennsylvania

September 15-16, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee

GUEST SPEAKER PRESENTATIONS (CONT.)

The Challenges of Conducting Opioid
Clinical Trials in Pediatrics

Steven J. Weisman, MD
Jane B. Pettit Chair in Pain Management
Children's Hospital of Wisconsin
Professor of Anesthesiology and Pediatrics
Medical College of Wisconsin

Opioid Misuse and Opioid Use Disorders in
Adolescents

Sharon Levy, MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Director, Adolescent Substance Abuse Program
Boston Children's Hospital

Clarifying Questions

ADJOURNMENT

Day 2: Friday, September 16, 2016

Call to Order and Introduction of the
Committees

Raeford E. Brown Jr., MD, FAAP
Chairperson, AADPAC

Conflict of Interest Statement

Stephanie L. Begansky, PharmD
Designated Federal Officer, DSARM

FDA Introductory Remarks

Sharon Hertz, MD
Director
DAAAP, ODE-II, OND, CDER, FDA

Clarifying Questions

OPEN PUBLIC HEARING

Break

Charge to the Committee

Sharon Hertz, MD

Questions to the Committee/Discussion

LUNCH

Questions to the Committee/Committee
Discussion (cont.)

BREAK

Questions to the Committee/Committee
Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss safety concerns associated with the use and study of opioids in pediatric patients and whether patient selection or management of these risks should differ from adults. Include in the discussion the safety of opioid analgesics in pediatric patients in terms of adverse events, as well as risks of misuse, abuse, addiction, overdose, and death.

Committee Discussion: The committee concurred that safety concerns associated with the use and study of opioids in pediatric patients do exist. The committee made it clear that there should be a balance in providing pain control for pediatric populations and making this population safe from the risks of misuse, abuse, addiction, overdose, and death. The committee stated that there is a need to understand the opioids better in general so that treatment in pediatrics can be scientifically based. Many committee members expressed that the information available to inform best practice such as pharmacokinetic data, safety data, and efficacy data, is not available. It was also stated that “pediatrics” defines a wide range of patients, and defining these populations better would allow for an improved approach to the safety issues that are most relevant to that specific sub-population. Additionally, it was suggested that current data networks be utilized to help analyze existing data, follow up patients to assess longer term safety outcomes and recruit patients for future trials. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Clinical trials ideally enroll the target population for the study drug. Discuss the important factors that clinicians should incorporate into their decision to prescribe opioid analgesics in pediatric patients taking into consideration medical conditions, safety, and other factors you believe are important for proper patient selection.

Committee Discussion: It was the consensus of the committee that clinicians should be incorporating patient and family education into their decisions to prescribe opioid analgesics to the pediatric population. Discussion surrounding screening and assessment tools when prescribing opioids took place and it was the suggestion of the committee that these tools are required and that family members of pediatric patients understand what they are to do if they have an issue or question. Some committee members suggested that a history of mental illness, misuse, and family history of opioid and alcohol use also be considered. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Studies of immediate-release opioid analgesics are generally conducted in patients with acute painful conditions, including post-operative pain as well as traumatic or other painful conditions that require opioid analgesia and are expected to be of a relatively short duration.

Studies of extended-release opioid analgesics are generally conducted in patients expected to require opioid treatment for at least 2 weeks who have pain severe enough to require an opioid, such as cancer pain, post-surgical pain for major procedures (i.e., major orthopedic surgeries), sickle-cell pain and others. Pediatric patients in studies of extended-release

opioids are required to have received opioids for a period of time prior to entering the study to assure that they tolerate the lowest available strength of the ER opioid.

Discuss incorporating the factors identified in Discussion #2 into the pediatric populations selected for the study of opioid analgesics.

Committee Discussion: *The committee stated that incorporating pediatric populations into research design has been demonstrated to be difficult and will certainly continue to be difficult, but must be considered. The committee identified issues that must be utilized in design, including safety issues both acute and chronic, for example, acute respiratory depression and the chronic use on opioids on developing brain. The committee stated that it was important to evaluate whether the clinical condition will even respond to opioids. They also suggested that it is important to evaluate the trial design to be certain that they are designed in a way that is relevant to a clinical condition in pediatric populations and to determine whether or not it is necessary to screen for risk factors such as potential for future addiction or diversion of supply. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** As you have heard, extrapolation of efficacy from adults to pediatric patients down to 2 years of age is utilized in the development of opioid analgesics. We have had situations where the PK in pediatric patients was not similar to adults, as would have been expected. In this situation, would it be appropriate to identify a safe starting dose that would be titrated to effect, or should efficacy be evaluated?

Committee Discussion: *The committee stated that the examination of pharmacokinetic data relating to opioid analgesics will need to be viewed in a unique way and may combine the use of known data for starting doses with extrapolation to other populations. The committee indicated that this will require many individuals and may be inaccurate in smaller populations. They also opined that opioids may be a special case where extrapolation doesn't apply for all patients and for all drug and that those indications we may need more complete data and even larger studies. The committee stated that another approach would be to use the currently available literature to define an initial dose and then build a more complete matrix that reflects safety and efficacy for a larger group of patients. Some committee members specified that the inpatient setting may be the only way to get these large numbers of patients. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION:** You have heard about significant challenges associated with the study of opioid analgesics in pediatric patients. Discuss possible approaches to overcome these challenges.

Committee Discussion: *The committee discussed possible approaches to overcome the significant challenges associated with the study of opioid analgesics in pediatric populations. They stated that some of these challenges are related to the funding of these studies along with the fears of investigators being stigmatized because of studying a pediatric population. In terms of funding, the committee suggested that the National Institutes of Health be a*

September 15-16, 2016

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee

source that is looked into for a coordinated effort. The committee also stated that incentivizing industry greater may help to solve this problem. Additionally, the committee suggested that the American Academy of Pediatrics may be a useful resource to help market the need for these types of studies in a pediatric population as certain conditions such as cancer, sickle cell anemia, and other terminal illnesses absolutely require opioids. The committee proposed identifying existing data sources and consortia as a good starting point in identifying what populations and at what doses current opioids are already being used. Please see the transcript for details of the committee discussion.

- 6. DISCUSSION:** Provide additional comments that you believe are important to address issues related to the use and study of opioid analgesics in pediatric patients.

***Committee Discussion:** The committee stated that the most important issue to address related to the use and study of opioid analgesics in pediatric patients was the need for data. They suggested that they specifically would like to see more comprehensive current use patterns and outcomes data. The committee also discussed the desire for Centers for Disease Control and Prevention guidelines and the Risk Evaluation and Mitigation Strategies to include specific pediatric population information. The committee also discussed the need for additional education to patients and providers on the proper disposal of opioid products. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:10 p.m. on September 15, 2016 and 2:10 p.m. on September 16, 2016.