Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Joint Meeting March 13-14, 2017

Location: Tommy Douglas Conference Center, 10000 New Hampshire Avenue, Silver Spring, Maryland.

Topic: On March 13 and 14, 2017, the committees discussed safety issues for new drug application (NDA) 201655, OPANA ER (oxymorphone hydrochloride) Extended-release Tablets, by Endo Pharmaceuticals Inc., with the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is an approved extended-release (ER) formulation intended to have abuse-deterrent properties based on its physicochemical properties, however, this information is not currently reflected in product labeling. The committees discussed pre- and post-marketing data about the abuse of OPANA ER, and the overall risk-benefit of this product. The committees also discussed abuse of generic oxymorphone ER and oxymorphone immediate-release (IR) products.

These summary minutes for the March 13-14, 2017, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration were approved on March 24, 2017.

I certify that I attended the March 13-14, 2017, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	/s/
Stephanie L. Begansky, PharmD	Almut Winterstein, PhD
Designated Federal Officer, AADPAC	Chairperson, DSaRM

Summary Minutes of the
Joint Meeting of the Drug Safety and Risk Management Advisory Committee
and the Anesthetic and Analgesic Drug Products Advisory Committee
March 13-14, 2017

The following is the final report of the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee, held on March 13-14, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Office of Safety and Epidemiology, the Division of Analgesia, Anesthesia and Addiction Products, and posted on the FDA website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm486856.htm and http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm486848.htm.

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

The Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on March 13-14, 2017, at the Tommy Douglas Conference Center, 10000 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Endo Pharmaceuticals Inc. The meeting was called to order by Almut G. Winterstein, RPh, PhD, FISPE (Chairperson). The conflict of interest statement was read into the record by Stephanie Begansky, PharmD (Designated Federal Officer). There were approximately 300 people in attendance on day 1 and approximately 150 people on day 2. There were 15 Open Public Hearing (OPH) speaker presentations.

Issue: The committees discussed safety issues for new drug application (NDA) 201655, OPANA ER (oxymorphone hydrochloride) Extended-release Tablets, by Endo Pharmaceuticals Inc., with the indication of management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is an approved extended-release (ER) formulation intended to have abuse-deterrent properties based on its physicochemical properties, however, this information is not currently reflected in product labeling. The committees discussed pre- and post-marketing data about the abuse of OPANA ER, and the overall risk-benefit of this product. The committees also discussed abuse of generic oxymorphone ER and oxymorphone immediate-release (IR) products.

Attendance:

Drug Safety and Risk Management Advisory Committee Members Present (Voting):
Tobias Gerhard, PhD, RPh; Suzanne B. Robotti (Consumer Representative); Anne-Michelle Ruha, MD, FACMT; Linda Tyler, PharmD, FASHP; Terri L. Warholak, PhD, RPh, FAPhA; Almut Winterstein, RPh, PhD, FISPE (Chairperson)

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

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

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

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

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): W. Joseph Herring, MD, PhD (Industry Representative) (*via telephone on day 2*)

Temporary Members (Voting): Jane B. Acri, PhD (*via telephone on day 2*); Warren B. Bilker, PhD; Daniel Ciccarone, MD, MPH; Marc G. Ghany, MD, MHSc; Ronald S. Litman, DO; Vincent Lo Re III, MD, MSCE; John Mendelson, MD; Laura D. Porter, MD (Patient Representative); Enrique F. Schisterman, PhD; Soko Setoguchi, MD, DrPH; James H. Woods, PhD; Eric D. Wish, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

FDA Participants (Non-Voting): Sharon Hertz, MD; Ellen Fields, MD, MPH; Judy Staffa, PhD, RPh; Silvia N. Calderon, PhD; Jana McAninch, MD, MPH, MS

Open Public Hearing Speakers: Emily Walden; Shruti Kulkrani (Center for Lawful Access and Abuse Deterrence) – *statement read by DFO*; Bob Twillman, PhD (Academy of Integrative Pain Management); Wade Delk and Melanie Simpson (American Society for Pain Management Nursing); Edwin R. Thompson (Pharmaceutical Manufacturing Research Services, Inc.); Sid Wolfe (Public Citizen); Megan Polanain, PhD (National Center for Health Research Cancer Prevention and Treatment Fund); Dan Cohen (Abuse Deterrent Coalition); Brooks Bono – *statement read by DFO*; Orvalene Prewitt – *statement read by DFO*; Gail Cawkwell and Paul Coplan (Purdue Pharma); Andrew Kolodny (Physicians for Responsible Opioid Prescribing) **–** *statement read by DFO*; Joe Adams (National Physicians Alliance); Bob Twillman, PhD on behalf of Charles Argoff; Michael Lissner and Barbara Lissner – *statement read by DFO*

The agenda was as follows:

Day 1: Monday, March 13, 2017

Call to Order and Introduction of Committee	***Almut Winterstein, RPh, PhD, FISPE*** *Chairperson, DSaRM*
Conflict of Interest Statement	***Stephanie L. Begansky, PharmD*** *Designated Federal Officer, AADPAC*

FDA Introductory Remarks	***Judy Staffa, PhD, RPh*** *Associate Director for Public Health Initiatives* *Office of Surveillance and Epidemiology (OSE), CDER, FDA*
INDUSTRY PRESENTATIONS	***Endo Pharmaceuticals Inc.***
Introduction	***Harris Rotman, PhD*** *Vice President, US Regulatory Affairs* *Endo Pharmaceuticals Inc.*
Pain, Opioid Therapy, and Personalized Medicine	***Perry G. Fine, MD*** *Professor of Anesthesiology* *University of Utah*
Decision-Making with Incomplete Observational Data	***Alexander M. Walker, MD, DrPH*** *Principal* *World Health Information Science Consultants*
Post-Marketing Safety and Observational Data: Category 4 Abuse Epidemiology	***Neil Shusterman, MD*** *Chief Medical Officer* *Endo Pharmaceuticals Inc.*
Epidemiology of Opana ER in Context	***Richard C. Dart, MD, PhD*** *RADARS® System* *Rocky Mountain Poison & Drug Center* *Professor, University of Colorado*
BREAK	
Clarifying Questions	
LUNCH	
FDA PRESENTATIONS	
Overview	***Judy Staffa, PhD, RPh***
Regulatory History of Opana ER	***Ellen Fields, MD, MPH*** *Deputy Director* *Division of Anesthesia, Analgesia and Addiction Products (DAAAP)* *Office of Drug Evaluation II (ODE-II)* *Office of New Drugs (OND), CDER, FDA*
In Vitro Abuse Deterrent Studies of Opana ER	***Erika E. Englund, PhD*** *CMC Reviewer* *New Drugs Branch II (NDB-II)* *Division of New Drug API (DNDAPI)* *Office of New Drug Products (ONDP)* *Office of Pharmaceutical Quality (OPQ), CDER, FDA*
Intranasal Studies for Opana ER and Integration of In Vitro Findings	***James M. Tolliver, PhD*** *Pharmacologist* *Controlled Substance Staff (CSS), CDER, FDA*

Drug Utilization Patterns for Oxymorphone ER and Selected Opioid Analgesics, 2009-2015	***Corinne Woods, RPh, MPH*** *Drug Utilization Analyst* *Division of Epidemiology II (DEPI-II)* *Office of Pharmacovigilance and Epidemiology (OPE)* *OSE, CDER, FDA*

Clarifying Questions

GUEST SPEAKER PRESENTATION

The 2015 Indiana HIV Outbreak: Overview	***Jerome Adams, MD, MPH*** *State Health Commissioner* *Indiana State Department of Health*

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) PRESENTATION

CDC Outbreak Investigations Involving Opana ER	***John T. Brooks, MD*** *Senior Medical Advisor* *Division of HIV/AIDS Prevention* *Centers for Disease Control and Prevention (CDC)*

FDA PRESENTATIONS

Opana ER Adverse Event Reports: Non-Oral Abuse and Thrombotic Microangiopathy	***Chaitali Patel, PharmD, BCPS*** *Safety Evaluator* *Division of Pharmacovigilance II (DPV-II)* *OPE, OSE, CDER, FDA*
Mechanisms Underlying Thrombotic Microangiopathy Associated with Intravenous Opana ER Abuse	***Ryan Hunt, MD*** *ORISE Fellow* *Division of Plasma Protein Therapeutics (DPPT)* *Office of Tissues and Advanced Therapies (OTAT)* *Center for Biologics Evaluation and Research (CBER), FDA*

Clarifying Questions

BREAK

FDA PRESENTATIONS

Statistical Considerations for Evaluating the Abuse-Related Outcomes of Reformulated Opana ER	***Diqiong Xie, PhD*** *Mathematical Statistician* *Division of Biometrics VII (DB-VII)* *Office of Biostatistics (OB)* *Office of Translational Sciences (OTS), CDER, FDA*
Review of Postmarketing Epidemiologic Data on Opana ER and Selected Comparators	***Jana McAninch, MD, MPH, MS*** *Medical Officer/Epidemiologist* *DEPI-II, OPE, OSE, CDER, FDA*

Clarifying Questions

ADJOURNMENT

Day 2: Tuesday, March 14, 2017

Call to Order and Introduction of Committee	***Almut Winterstein, MD*** *Chairperson, DSaRM*
Conflict of Interest Statement	***Stephanie L. Begansky, PharmD*** *Designated Federal Officer, AADPAC*
FDA Introductory Remarks	***Judy Staffa, PhD, RPh*** *Associate Director for Public Health Initiatives* *Office of Surveillance and Epidemiology (OSE), CDER, FDA*
OPEN PUBLIC HEARING	
LUNCH	
Charge to the Committee	***Judy Staffa, PhD, RPh***
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion (cont.)	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Please discuss the strengths and limitations of the experimental and epidemiologic data regarding the safety concerns with reformulated Opana ER, including:

   A. The observed shift in abuse patterns from the nasal to injection route of abuse, and

   B. Reports of a TTP-like illness and HIV transmission associated with intravenous abuse of this drug

   How do the data inform our understanding of the risk/benefit balance for Opana ER, relative to other oxymorphone products?

   Committee Discussion: *The majority of the committee concurred that the totality of evidence shows that a shift in the abuse pattern of Opana ER from the nasal to injection route (IV) of abuse occurred following its reformulation. The committee agreed that the data demonstrate that reformulated Opana ER does not resist preparation for injection adequately, and represents a problem because of the apparent greater proportion of drug abuse by the injection route compared with other opioids. The committee also agreed that the high street cost of the product coupled with the method of preparation contributed to IV users sharing the drug solution and the equipment used to prepare and inject it, made worse by the large*

number of injections per day. These factors likely contributed to the outbreak of HIV and HCV infections in Indiana. The committee agreed that cases of TTP-like illness in Tennessee were likely to have been specifically caused by intravenous exposure to the excipient, PEO. However, the committee stated the need for more and better epidemiological studies in the appropriate patient populations to quantify the risk of Opana ER. Regarding attributing the risks to reformulated Opana ER relative to other oxymorphone products, the committee stated that the current epidemiological data do implicate reformulated Opana ER, but emphasized that the studies suggest that oxymorphone ER generic products were also being abused at high rates by both the intranasal and IV routes. The committee suggested that cohort studies of users of Opana ER, and their response to the reformulation of the product, might have helped to make the data more compelling; however, the challenges of actually collecting such data were also noted. Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Please discuss any potential consequences of taking regulatory action(s) relating to reformulated Opana ER, such as effects on prescribing or abuse patterns for other products, including other oxymorphone products.

   Committee Discussion: *The committee concurred that patients abusing opioids will find something else to abuse if Opana ER is not available. They stated that the alternative might be safer than reformulated Opana ER in IV abusers, however, there was no way to predict the effects of regulatory actions. The committee agreed that generic oxymorphone ER products were also being abused by both the intranasal and IV routes. Several committee members questioned the role of Opana ER and oxymorphone in pain management, whilst several other committee members recommended that restrictions be placed on oxymorphone's indication and prescribing, such as not to be prescribed as a first line therapy or that only certain physicians should be able to prescribe it to a defined subset of patients. Committee members suggested that restricting prescribing and patient access might in itself reduce street availability for abuse. Other committee members acknowledged that there are instances in pain management where use of oxymorphone is useful, such as patients with possible risks for pharmacokinetic drug-drug interactions. Several committee members noted that regulating the drug in terms of abuse potential versus the intended use of the product is difficult. Some committee members thought that a more specific risk evaluation and mitigation strategy (REMS) may decrease the risk of abuse and IV administration of this product, and oxymorphone products in general, whereas other committee members doubted the ability of either labeling or REMS to mitigate the risk of abuse and related adverse health effects. Please see the transcript for details of the committee discussion.*

3. **VOTE**: Do the benefits of reformulated Opana ER continue to outweigh its risks?

   Vote Result: Yes: 8 No: 18 Abstain: 1

   Committee Discussion: *The majority of the committee voted "No," indicating their belief that the benefits of reformulated Opana ER do not continue to outweigh its risks. The committee members who voted "No" were split with regard to whether the unintended consequences associated with Opana ER were sufficient to warrant removal from the*

market. Some members stated that, at the very least, a restrictive REMS should be put into place to limit prescribing. Those members who voted "Yes" acknowledged the risks with this formulation; however, also recognized that certain subpopulations of patients clearly benefit from this product being available on the market. The committee member who abstained stated that data were not provided to fairly evaluate the risk/benefit ratio of the product as most of the committee discussion surrounded only risk. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 5:10 p.m. on March 13, 2017 and 4:10 p.m. on March 14, 2017.