Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Joint Meeting
July 26, 2017

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

Topic: On July 26, 2017, the committees new drug application (NDA) 209653, for oxycodone hydrochloride extended-release oral tablets, submitted by Intellipharmaceutics Corp., with the proposed indication of management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product. The committees will be asked to discuss the overall risk-benefit profile of the product, and whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling.

These summary minutes for the July 26, 2017, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration were approved on August 12, 2017.

I certify that I attended the July 26, 2017, joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Moon Hee V. Choi, PharmD
Acting Designated Federal Officer, AADPAC

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

Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Joint Meeting
July 26, 2017

The following is an internal report (which has not been reviewed) of the joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, held on July 26, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Surveillance and Epidemiology, and posted on the FDA website at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm536646.htm and
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm536632.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 (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on July 26, 2017, 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 and Intellipharmaceutics Corp. 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 Moon Hee Choi, PharmD (Acting Designated Federal Officer). There were approximately 75 people in attendance. There were eight Open Public Hearing (OPH) speaker presentations.

Issue: The committees discussed new drug application (NDA) 209653, for oxycodone hydrochloride extended-release oral tablets, submitted by Intellipharmaceutics Corp., with the proposed indication of management of moderate-to-severe pain when a continuous around the clock analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product. The committees were asked to discuss the overall risk-benefit profile of the product, and whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting):
Raeford E. Brown, Jr., MD, FAAP (Chairperson); David S. Craig, PharmD; Jeffrey L. Galinkin, MD, FAAP; Jennifer G. Higgins, PhD (Consumer Representative); Ronald S. Litman, DO; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; Lonnie Zeltzer, MD

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

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Brian T. Bateman, MD, MSc; Anita Gupta, DO, PharmD

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Laurel A. Habel, MPH, PhD; Steven B. Meisel, PharmD; Suzanne B. Robotti (Consumer Representative); Christopher H. Schmid, PhD; Soko Setoguchi, MD, DrPh; Terri L. Warholak, PhD, RPh, FAPhA

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Denise M. Boudreau, PhD, RPh; Niteesh K. Choudhry, MD, PhD; Anne-Michelle Ruha, MD, FACMT; Almut Winterstein, RPh, PhD, FISPE (Chairperson)

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

Temporary Members (Voting): Cynthia Arfken, PhD; Melinda Campopiano, MD; Tobias Gerhard, BSPharm, PhD, FISPE; Elizabeth A. Joniak-Grant, PhD (Patient Representative); Richard Kline, PhD; John Mendelson, MD; Lewis S. Nelson, MD; Scott Novak, PhD, MSc

FDA Participants (Non-Voting): Sharon Hertz, MD; Ellen Fields, MD, MPH; Judy Staffa, PhD, RPh; James Tolliver, PhD

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

Open Public Hearing Speakers: Megan Polanin, PhD (National Center for Health Research Cancer Prevention and Treatment Fund); Dan Cohen (Abuse Deterrent Coalition); Charlie Cichon (National Association of Drug Diversion Investigators); Fred Wells Brason II (Project Lazarus); Bob Twillman, PhD, FAPM (Academy of Integrative Pain Management, formerly American Academy of Pain Management); Michael Johnson, MD; Sidney Wolfe (Public Citizen); Edwin Thompson (Pharmaceutical Manufacturing Research Service, Inc.)

The agenda was as follows:

Call to Order and Introduction of Committee	**Raeford E. Brown, Jr., MD, FAAP** Chairperson, AADPAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Acting 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
APPLICANT PRESENTATIONS	**Intellipharmaceutics Corporation**
Introduction	**Isa Odidi, PhD** Chairman, CEO, co-CSO, and co-Founder Intellipharmaceutics Corp.
Need for Abuse-Deterrent Opioid Analgesics	**Richard Dart, MD, PhD** Director, Rocky Mountain Poison and Drug Center Professor, University of Colorado Executive Director of the RADARS® System
Clinical Pharmacology	**Beatrice Setnik, PhD** Vice President for Scientific & Medical Affairs INC Research, LLC. Adjunct Professor Department of Pharmacology and Toxicology University of Toronto
Category 1 Abuse-Deterrent Studies	**Edward Cone, PhD** Principal Scientist PinneyAssociates Bethesda, MD Adjunct Professor of Psychiatry and Behavioral Sciences (PT) Johns Hopkins Medicine Baltimore, MD
Public Health Perspective	**Edward Sellers, MD, PhD, FRCPC, FACP** President and Principal, DL Global Partners Inc. Professor Emeritus, Pharmacology, Medicine & Psychiatry University of Toronto
Clarifying Questions	
Break	

FDA PRESENTATIONS

Need for Human Abuse Potential Studies for Evaluation of NDA 209-653	**James Tolliver, PhD** Pharmacologist Controlled Substance Staff Office of the Center Director, CDER, FDA

FDA PRESENTATIONS (CONT.)

Utilization Trends of Oxycodone ER and Other Extended-Release/Long-Acting Opioid Analgesics, 2012-2016	**Jennie Wong, PharmD** Drug Utilization Analyst Division of Epidemiology II Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology CDER, FDA
Excipients in Oral Opioid Analgesics and IV Abuse – A Regulatory Perspective	**Ellen Fields, MD, MPH** Deputy Director DAAAP, ODE II, OND, CDER, FDA
Clarifying Questions	

GUEST SPEAKER PRESENTATION

Excipient Harms and Tampering of Opioid Analgesics	**Nabarun Dasgupta, MPH, PhD** Epidemiologist Injury Prevention Research Center Department of Epidemiology Eshelman School of Pharmacy University of North Carolina Chapel Hill, NC
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

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** The Applicant submitted only Category 1 (in vitro) studies to support labeling of Oxycodone HCl ER tablets for abuse deterrence, and is seeking labeling for abuse-deterrent properties only for the IV route of abuse. The product contains excipients that are intended to deter abuse by other routes. Discuss whether it is appropriate to consider labeling this product for abuse-deterrent properties for a single route without a complete assessment of all relevant routes of abuse.

   Committee Discussion*: The majority of the committee agreed that it was not appropriate to consider labeling this product with abuse-deterrent properties for a single route without a complete assessment of all relevant routes of abuse. The majority of the committee also agreed Category 2 and Category 3 studies are necessary to complete the assessment of abuse-deterrent properties. The committee agreed with the need for the sponsor to conduct further studies in accordance with the Guidance for Industry on Abuse Deterrent Opioids, as the sponsors of the other approved products with labeling for abuse deterrent properties have done. Some committee members agreed that without such a complete assessment,there would likely be confusion among health care providers and patients who might think that the product could deter abuse through other routes of administration. In addition,this could create difficulty for prescribers to determine if there was a risk that the product would be abused only intravenously, and not by other routes. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** As presented earlier today, excipients in a drug product must have a purpose, and many oral formulations have excipients that pose health risks if injected. As discussed at previous advisory committee meetings, there have been concerns raised that the presence of excipients in abuse-deterrent formulations of products intended for oral use have resulted in additional toxicity to those who abuse these products by non-oral routes. This product contains a nasal irritant, SLS, and a blue dye, that, according to the Applicant, are intended to deter abuse by the nasal and oral routes, however, no data have been provided to support these claims.

   a. Discuss any concerns you may have regarding this product and the presence of excipients that have been included to deter abuse.

   b. Discuss whether it is acceptable to include excipients in this product that increase the potential risk to those who may abuse the drug via certain non-IV routes of abuse, and that have not been shown or are not intended to contribute to the proposed IV abuse-deterrent claim being sought by the Applicant.

c. Discuss whether it is possible to determine an acceptable level of risk for excipients that may be toxic by unintended routes of administration for this product?

***Committee Discussion**: The majority of the committee members agreed that there were concerns regarding the safety and the potential toxicity that may be caused by the excipients that have been included to deter abuse. Some committee members commented that some of the excipients in this product act as active pharmacological agents and dose-response data should be required like with other active pharmacologic ingredients. Additionally, most committee members had major concerns regarding the effects the blue dye would have when ingested and used in large amounts, and stated the need for long term data on various body sizes as well as how it will affect the GI system. Some committee members expressed concerns about the lack of data on whether the blue dye excipient would actually deter abuse, and pointed out that it may attract abusers. One committee member suggested the need for data examining tolerability to the increased viscosity of this product among patients who use it orally as directed. One committee member expressed concerns that it was inappropriate to use blue dye to stain and shame abusers, noting that addiction is a mental illness. Overall, the committee noted that there has been no assessment for benefit or harm of the blue dye when taken orally or when abused nasally or intravenously, and that there is no evidence of proven deterrent effect of the blue dye. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Although the Applicant is not currently seeking a nasal or oral abuse-deterrent claim, discuss the type of data that would be necessary to support a claim that blue dye has deterrent effects for the intravenous, nasal, or oral routes of abuse for this product. Discuss if it is acceptable to predict intranasal or oral abuse-deterrent effects from Category 1 studies alone for this product.

***Committee Discussion**: The majority of the committee stated that it was not acceptable to predict intranasal or oral abuse-deterrent effects from Category 1 studies alone for this product and agreed on the need for Category 2 and 3 studies. These committee members also agreed that the best way to evaluate abuse-deterrent properties would be to use the guidance provided by the FDA. Some committee members suggested the use of dose-response curves and drug liking studies., It was recommended that the Sponsor conduct Category 1-like studies examining the use of household chemicals other than water for the removal of the blue dye from the skin., It was also suggested that opioid users be interviewed and focus groups be used to document attitudes and opinions regrading whether or not the blue dye might have deterrent effects for the intravenous, nasal, or oral routes of abuse for this product. Other committee members suggested studying how this product actually deterred abuse in potential users and current opioid abusers. Please see the transcript for details of the committee discussion.*

4. **VOTE**: Has the Applicant demonstrated that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration?

Vote Result: Yes: 4 No: 19 Abstain: 0

Committee Discussion*: The majority of the committee agreed that the Applicant did not demonstrate that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration. Some committee members who voted "Yes" noted that they voted based on the strict interpretation of the question and not in the full context of drug product. Some committee members who voted "Yes" also noted that it can be expected to deter abuse because of the difficulty in syringabillity of the drug product since it becomes highly viscous. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Are there sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration?

   Vote Result: Yes: 0 No: 23 Abstain: 0

   Committee Discussion*: The committee unanimously agreed that there are not sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration. The majority of committee members agreed that Category 2 and 3 studies as well as human safety data are needed to make a determination on labeling this drug product as abuse deterrent. Please see the transcript for details of the committee discussion.*

6. **VOTE:** Should this drug product, Oxycodone HCl ER tablets, be approved?

   Vote Result: Yes: 1 No: 22 Abstain: 0

   Committee Discussion: *The majority of the committee agreed that the product, Oxycodone HCL ER tablets, should not be approved. The majority of the committee agreed that safety and efficacy data for patient oral use, as well as in reference to all routes of abuse are needed to approve Oxycodone HCl ER tablets. The committee member who voted "Yes" stated that despite concerns with the blue dye, he did not believe that this drug is any less safe than what is currently on the market. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:43 p.m.