Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
October 12, 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 new drug application (NDA) 209128, sufentanil sublingual tablets, submitted by AcelRx Pharmaceuticals, Inc., for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The committee discussed risk-benefit considerations and whether this product should be approved.

These summary minutes for the October 12, 2018 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration were approved on December 7, 2018.

I certify that I attended the October 12, 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	Kevin Zacharoff, MD, FACIP, FACPE, FAAP
Designated Federal Officer, AADPAC	Acting Chairperson, AADPAC

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
October 12, 2018

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 12, 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 and AcelRx Pharmaceuticals, Inc. The meeting was called to order by Kevin Zacharoff, MD, FACIP, FACPE, FAAP (Acting Chairperson). The conflict of interest statement was read into the record by Moon Hee Choi, PharmD (Designated Federal Officer). There were approximately 95 people in attendance. There were nine 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 new drug application (NDA) 209128, sufentanil sublingual tablets, submitted by AcelRx Pharmaceuticals, Inc., for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The committee discussed risk-benefit considerations and whether this product should be approved.

Attendance:
Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Ronald S. Litman, DO, ML; Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP (Acting Chairperson); Lonnie Zeltzer, MD

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): Brian T. Bateman, MD, MSc; Raeford E. Brown, Jr., MD, FAAP (Chairperson); Basavana G. Goudra, MD, FRCA, FCARSCI; Mary Ellen McCann, MD, MPH

Temporary Members (Voting): Michael Fischer, MD, MS; Jennifer Higgins, PhD (Acting Consumer Representative); Alan Kaye, MD, PhD; Steven B. Meisel, PharmD, CPPS; Joseph P. O'Brien, MBA (Patient Representative); Marjorie Shaw Phillips, MS, RPh, FASHP, CIP; Gregory Terman, MD, PhD; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA; Jacqueline A.M. Willacy, RN

FDA Participants (Non-Voting): Sharon Hertz, MD; Janet Maynard, MD, MHS; Ning Hu, MD, MS; Cynthia LaCivita, PharmD; Irene Chan, PharmD, BCPS

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

Open Public Hearing Speakers: Timothy Ekola, BSPharm, PharmD; Mike Ritter,MD, FACEP; Fredrick H. Bender, PharmD; Maria Foy, PharmD; Harold S. Minkowitz, MD; Meena M. Aladdin, MS, PhD (Public Citizen Foundation); Jacob Hutchins, MD; Lynn Webster, MD; Varuna Srinivasan, MBBS, MPH (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	**Kevin Zacharoff, MD, FACIP, FACPE, FAAP** 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
APPLICANT PRESENTATIONS	**AcelRx Pharmaceuticals, Inc.**
Introduction/Overview of DSUVIA	**Pamela Palmer, MD, PhD** Chief Medical Officer AcelRx Pharmaceuticals, Inc.
Unmet Need	**James Miner, MD** Chief of Emergency Medicine Hennepin County Medical Center
Clinical Pharmacology of Sublingual Sufentanil	**Dennis Fisher, MD** Founder *P Less Than* Pharmacometric Consulting Professor (Emeritus), Department of Anesthesia University of California, San Francisco
Efficacy	**Pamela Palmer, MD, PhD**
Safety	**Neil Singla, MD** Chief Scientific Officer Lotus Clinical Research, LLC
Benefit/Risk Conclusion	**Pamela Palmer, MD, PhD**
Clarifying Questions	
BREAK	

FDA PRESENTATIONS

Introduction and Review of Clinical Safety and Efficacy	**Ning Hu, MD, MS** Clinical Reviewer DAAAP, ODE-II, OND, CDER, FDA
Human Factors Evaluation	**Otto L. Townsend, PharmD** Team Leader Division of Medication Error Prevention and Analysis Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Risk Evaluation and Mitigation Strategies (REMS) Considerations	**LaShaun Washington-Batts, PharmD** Reviewer Division of Risk Management OMEPRM, OSE, CDER, FDA
Benefit/Risk Considerations	**Ning Hu, MD, MS**
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:** Discuss whether the data are adequate to support a finding of efficacy for sufentanil sublingual tablets 30 mcg for the proposed indication: the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting.

***Committee Discussion**: The majority of the committee members stated that the data supported the finding that sufentanil sublingual tablets 30 mcg are effective in the treatment of pain when compared to placebo. Several committee members added that this medication would be beneficial in treating acute pain for patients without intravenous access or those patients who are unable to swallow. However, several other committee members raised concerns regarding the lack of active comparator efficacy studies with existing opioid and non-opioid standards of care. Some committee members added that the median peak onset of action of one hour is relatively slow for the treatment of acute breakthrough pain and may not represent a significant advantage over existing treatments. One committee member expressed concerns with the lack of ability to titrate due to the fixed dosing scheme and the inability to make dose adjustments based on a patient's weight. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Based on the available safety data, discuss any concerns you may have about the safety profile of sufentanil sublingual tablets 30 mcg.

***Committee Discussion**: Several committee members expressed concern with the lack of safety data in elderly patients as the patients in the study were mostly younger patients. One committee member added that elderly patients generally have decreased weight and drug clearance so use of sufentanil should be limited to patients under 65 years of age if approved. Other committee members expressed concern that the proposed fixed dosing scheme does not recommend dosing adjustments based on weight or age. One committee member disagreed by stating that sufentanil was not any more dangerous than other stronger medications that is given intravenously. Some committee members raised concern with the one-hour dosing interval for this medication, with one committee member noting how labor intensive it would be for nursing staff to administer, document administration, and monitor the patient hourly. Some committee members noted the issue of not being able to give intravenous naloxone to reverse any potential overdose. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss whether data from the human factors studies and the clinical trials support the safe and effective use of the proposed product administered by healthcare professionals in certified settings such as hospitals, emergency departments, and surgical centers. In your discussion, consider whether the REMS proposed by FDA can be expected to mitigate the risks associated with dropped sufentanil tablets and including the risk of accidental exposure.

***Committee Discussion**: Overall, the committee members agreed that the proposed product and dispensing system is safe and effective for use by healthcare professionals in certified settings such as hospitals, emergency departments, and surgical centers. The committee members agreed that dropped tablets are unlikely with the proposed delivery system and if dropped tablets did occur, it would not likely pose a threat to children or animals in the proposed usage settings. Overall, the committee members agreed with and supported the FDA's proposed REMS program for sufentanil sublingual tablets 30 mcg. However, one committee member expressed concern with the REMS requirement that every hospital must proactively educate nurses who will be administering this*

medication as the logistics of conducting this type of training within a large healthcare system would be challenging. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** Discuss any concerns you may have regarding the abuse or misuse of sufentanil sublingual tablets and whether, based on the available data, the benefits to patients are expected to outweigh public health risks related to abuse, misuse, and accidental exposure.

   ***Committee Discussion**: Overall, the committee members agreed that the benefits associated with sufentanil sublingual tablets outweighs the risks. Some committee members found it difficult to compare public health risk and its benefit as the study was performed only in hospital settings. Several committee members agreed that the abuse potential for this medication was evaluated to be similar to other Schedule II opioid medications. Other committee members stated that having a REMS program associated with this medication and its limited use in healthcare settings will further decrease the incidence and potential for abuse. One committee member stated that the abuse potential for this medication is likely lower than that of other controlled substances due to its unit-dose packaging and delivery system. However, several committee members expressed concern that if approved, sufentanil may eventually find use outside of healthcare settings and could potentially lead to inadvertent overdosing by patients due to improper timing of doses and dose-stacking. Please see the transcript for details of the committee discussion.*

5. **VOTE:** Overall, do the benefits of sufentanil sublingual tablets 30 mcg with the REMS proposed by FDA outweigh the risks for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting, supporting approval of sufentanil sublingual tablets 30 mcg?

   Vote Result: Yes: 10 No: 3 Abstain: 0

   ***Committee Discussion**: The majority of the committee members agreed that the benefits of sufentanil sublingual tablets 30 mcg with the REMS proposed by FDA outweigh the risks for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The committee members who voted "Yes" agreed that the presented data clearly showed efficacy in the treatment of acute moderate to severe pain. Some committee members added that the novel sublingual dosage form of this medication would fill an unmet medical need in terms of pain relief for patients without intravenous access, unable to swallow, or in certain military settings. One committee member stated that introducing this opioid medication to the market would pose minimal risk for abuse and diversion due to the proposed REMS program and limitation to use in healthcare settings only. Another committee member added that the lack of intravenous access for naloxone administration is a negligible concern since we administer many other oral opioids without intravenous access for naloxone administration. The*

committee members who voted "No" stated that there is lack of proven efficacy and necessity within the inpatient setting. These committee members agreed that the proposed patient population must be narrowed and more specifically defined. One committee member added that sufentanil would be the first opioid medication that does not have a direct conversion to morphine equivalents. Another committee member stated that the onset for this medication is too slow for the proposed indication of moderate-to-severe acute pain. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 3:02 p.m.