

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND ANALGESIC DRUGS PRODUCTS
ADVISORY COMMITTEE (AADPAC)

Thursday, October 12, 2018

8:00 a.m. to 3:03 p.m.

FDA White Oak Campus
Building 31, the Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland

1 **Meeting Roster**

2 **DESIGNATED FEDERAL OFFICER (Non-Voting)**

3 **Moon Hee V. Choi, PharmD**

4 Division of Advisory Committee and Consultant

5 Management

6 Office of Executive Programs, CDER, FDA

7

8 **ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY**

9 **COMMITTEE MEMBERS (Voting)**

10 **Ronald S. Litman, DO, ML**

11 Professor of Anesthesiology & Pediatrics

12 Perelman School of Medicine

13 University of Pennsylvania

14 Attending Anesthesiologist

15 The Children's Hospital of Philadelphia

16 Medical Director

17 Institute for Safe Medication Practices

18 Philadelphia, Pennsylvania

19

20

21

22

1 **Abigail B. Shoben, PhD**

2 Associate Professor, Division of Biostatistics

3 College of Public Health

4 The Ohio State University

5 Columbus, Ohio

6

7 **Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP**

8 *(Acting Chairperson)*

9 Faculty and Clinical Instructor

10 Pain and Medical Ethics

11 State University of New York, Stony Brook School of

12 Medicine, Stony Brook, New York

13 Ethics Committee Chair

14 St. Catherine of Siena Medical Center

15 Smithtown, New York

16

17

18

19

20

21

22

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Lonnie Zeltzer, MD

Director, Pediatric Pain and Palliative Care

Program

Division of Pediatric Hematology-Oncology

Distinguished Professor of Pediatrics,

Anesthesiology, Psychiatry and Biobehavioral

Sciences

David Geffen School of Medicine at UCLA

Los Angeles, California

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY

COMMITTEE MEMBER (Non-Voting)

W. Joseph Herring, MD, PhD

(Industry Representative)

Associate Vice President, Clinical Neuroscience

Merck Research Laboratories

North Wales, Pennsylvania

1 **TEMPORARY MEMBERS (Voting)**

2 **Michael Fischer, MD, MS**

3 Associate Professor of Medicine

4 Harvard Medical School

5 Associate Professor of Epidemiology

6 Harvard T.H. Chan School of Public Health

7 Division of Pharmacoepidemiology &

8 Pharmacoeconomics

9 Brigham & Women's Hospital

10 Boston, Massachusetts

11

12 **Jennifer Higgins, PhD**

13 *(Acting Consumer Representative)*

14 Director of Research & Policy

15 Association of Developmental Disabilities Providers

16 Framingham, Massachusetts

17

18 **Alan Kaye, MD, PhD**

19 Professor, Program Director, and Chair

20 Department of Anesthesiology

21 Louisiana State University

22 New Orleans, Louisiana

1 **Steven B. Meisel, PharmD, CPPS**

2 System Director of Medication Safety

3 Fairview Health Services/HealthEast Care System

4 Minneapolis, Minnesota

5

6 **Joseph P. O'Brien, MBA**

7 *(Patient Representative)*

8 President & Chief Executive Officer

9 National Scoliosis Foundation

10 Stoughton, Massachusetts

11

12 **Marjorie Shaw Phillips, MS, RPh, FASHP, CIP**

13 Pharmacy Coordinator

14 Clinical Research and Education

15 AU Medical Center at Augusta University

16 Clinical Professor of Pharmacy Practice (without
17 salary)

18 University of Georgia College of Pharmacy

19 Augusta, Georgia

20

21

22

1 **Gregory Terman, MD, PhD**

2 Professor

3 Department of Anesthesiology and Pain Medicine

4 and the Graduate Program in Neuroscience

5 University of Washington

6 Seattle, Washington

7

8 **Terri L. Warholak, PhD, RPh, CPHQ, FAPhA**

9 Professor and Assistant Dean

10 Academic Affairs and Assessment

11 College of Pharmacy

12 University of Arizona

13 Tucson, Arizona

14

15 **Jacqueline A.M. Willacy, RN**

16 Clinical Critical Care Nurse

17 Department of Veterans Affairs

18 Washington, District of Columbia

19

20

21

22

1 **FDA PARTICIPANTS (Non-Voting)**

2 **Sharon Hertz, MD**

3 Director

4 Division of Anesthesia, Analgesia and Addiction

5 Products (DAAAP)

6 Office of Drug Evaluation II (ODE-II)

7 Office of New Drugs (OND)

8 CDER, FDA

9

10 **Janet Maynard, MD, MHS**

11 Clinical Team Leader

12 DAAAP, ODE-II, OND, CDER, FDA

13

14 **Ning Hu, MD, MS**

15 Medical Officer

16 DAAAP, ODE-II, OND, CDER, FDA

17

18

19

20

21

22

1 **Cynthia LaCivita, PharmD**

2 Director

3 Division of Risk Management

4 Office of Medication Error Prevention and

5 Risk Management (OMEPRM)

6 OSE, CDER, FDA

7

8 **Irene Chan, PharmD, BCPS**

9 Deputy Director

10 Division of Medication Error Prevention and

11 Analysis

12 OMEPRM, OSE, CDER, FDA

13

14

15

16

17

18

19

20

21

22

1	C O N T E N T S	
2	AGENDA ITEM	PAGE
3	Call to Order and Introduction of Committee	
4	Kevin Zacharoff, MD, FACIP, FACPE, FAAP	12
5	Conflict of Interest Statement	
6	Moon Hee Choi, PharmD	17
7	FDA Opening Remarks	
8	Sharon Hertz, MD	21
9	Applicant Presentations - AcelRx	
10	Introduction/Overview of DSUVIA	
11	Pamela Palmer, MD, PhD	26
12	Unmet Need	
13	James Miner, MD	38
14	Clinical Pharmacology of	
15	Sublingual Sufentanil	
16	Dennis Fisher, MD	45
17	Efficacy	
18	Pamela Palmer, MD, PhD	52
19	Safety	
20	Neil Singla, MD	63
21	Benefit/Risk Conclusion	
22	Pamela Palmer, MD, PhD	71

1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE
3	Clarifying Questions	74
4	FDA Presentations	
5	Introduction and Review of Clinical	
6	Safety and Efficacy	
7	Ning Hu, MD, MS	124
8	Human Factors Evaluation	
9	Otto Townsend, PharmD	139
10	Risk Evaluation and Mitigation Strategies	
11	(REMS) Considerations	
12	LaShaun Washington-Batts, PharmD	149
13	Benefit/Risk Considerations	
14	Ning Hu, MD, MS	155
15	Clarifying Questions	157
16	Open Public Hearing	189
17	Charge to the Committee	
18	Sharon Hertz, MD	227
19	Questions to the Committee and Discussion	229
20	Adjournment	288
21		
22		

1 P R O C E E D I N G S

2 (8:00 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. ZACHAROFF: Good morning. Before we
6 begin, I would first like to remind everyone to
7 please silence your cell phones, smartphones, and
8 any other devices if you have not already done so.
9 Thank you. I would also like to identify the FDA
10 press contact, either Lyndsay Meyer or Michael
11 Felberbarum. If your present, please wave. Thank
12 you.

13 My name is Kevin Zacharoff. I am the acting
14 chairperson of the Anesthetic and Analgesics Drug
15 Products Advisory Committee, and I will be chairing
16 this meeting today. I will now call the meeting of
17 the Anesthetic and Analgesic Drug Products Advisory
18 Committee to order. We'll start by going around
19 the table and introducing ourselves. We'll start
20 with the FDA to my left and go around the table
21 from there. Thank you.

22 DR. HERTZ: Good morning. I am Sharon

1 Hertz. I'm the director for the Division of
2 Anesthesia, Analgesia, and Addiction Products here
3 at CDER.

4 DR. MAYNARD: Good morning. I'm Janet
5 Maynard. I'm a clinical team leader in the
6 Division of Anesthesia, Analgesia, and Addiction
7 Products.

8 DR. HU: Good morning. My name is Ning Hu,
9 medical officer from the Division of Anesthetic,
10 Analgesia, and Addiction Products, FDA.

11 DR. LaCIVITA: Good morning. My name is
12 Cynthia LaCivita. I'm the director of the Division
13 of Risk Management in the Office of Surveillance
14 and Epidemiology.

15 DR. CHAN: Good morning. My name is Irene
16 Chan, and I'm deputy director in the Division of
17 Medication Error Prevention and Analysis in the
18 Office of Surveillance and Epidemiology.

19 DR. MEISEL: Steve Meisel, director of
20 medication safety, Fairview Health Services,
21 Minneapolis, Minnesota.

22 MS. SHAW PHILLIPS: H. Marjorie Shaw

1 Phillips, pharmacy coordinator, clinical research
2 and education, AU Medical Center, Augusta
3 University, and also without salary, clinical
4 professor of pharmacy practice, UGA College of
5 Pharmacy, Augusta.

6 DR. FISCHER: I'm Mike Fischer. I'm an
7 internist and pharmacoepidemiology researcher at
8 Brigham Women's Hospital and Harvard Med School in
9 Boston.

10 DR. LITMAN: Ron Litman. I'm a
11 anesthesiologist at the Children's Hospital of
12 Philadelphia, University of Pennsylvania, and the
13 medical director of the Institute for Safe
14 Medication Practices.

15 DR. CHOI: Moon Hee Choi, designated federal
16 officer.

17 DR. ZACHAROFF: Once again, good morning.
18 My name is Kevin Zacharoff. I'm a physician with
19 expertise in anesthesiology and pain medicine, and
20 I am a faculty member and clinical instructor at
21 the Stony Brook School of Medicine in New York.

22 DR. ZELTZER: Hi. I'm Lonnie Zeltzer,

1 distinguished professor of pediatrics,
2 anesthesiology and psychiatry at UCLA School of
3 Medicine and director of the Pediatric Pain and
4 Palliative Care Program.

5 DR. SHOBNEN: Hi. I'm Abby Shoben. I'm an
6 associate professor of biostatistics at the Ohio
7 State University.

8 DR. KAYE: Good morning. I'm Alan Kaye.
9 I'm an anesthesiologist and a pain specialist and
10 professor, program director, and chairman at the
11 Louisiana State University Health Science Center in
12 New Orleans, Louisiana.

13 DR. TERMAN: Good morning. I'm Greg Terman.
14 I'm professor of anesthesiology and pain medicine,
15 the University of Washington, Seattle, and director
16 of the acute pain service at the University of
17 Washington Medical Center.

18 MS. WILLACY: Good morning. My name is
19 Jacqueline Willacy. I'm a critical care nurse at
20 the Washington DC VA. I'm here to represent
21 nurses.

22 DR. WARHOLAK: Good morning. I'm Terri

1 Warholak, and I'm a professor and assistant dean at
2 the university of Arizona, College of Pharmacy.

3 DR. HIGGINS: Jennifer Higgins. I'm the
4 AADPAC consumer representative, acting.

5 DR. O'BRIEN: Joe O'Brien, president and CEO
6 of the National Scoliosis Foundation in Stoughton,
7 Massachusetts. I am also a scoliosis patient who
8 had his sixth spinal fusion this past December, and
9 I am the patient representative.

10 DR. HERRING: Hello. Good morning. I'm Joe
11 Herring. I'm a neurologist and associate vice
12 president of clinical neuroscience at Merck and the
13 AADPAC industry representative.

14 DR. ZACHAROFF: Thank you all.

15 For topics such as those being discussed at
16 today's meeting mirror often a variety of opinions,
17 some of which are quite strongly held. Our goal at
18 today's meeting is that this will be a fair and
19 open forum for discussion of these issues and that
20 individuals can express their views without
21 interruption. Thus, as a gentle reminder,
22 individuals will be allowed to speak into the

1 record only if recognized by the chair. We look
2 forward to a productive meeting.

3 In the spirit of the Federal Advisory
4 Committee Act and the Government in the Sunshine
5 Act, we ask that the advisory committee members
6 take care that their conversations about the topic
7 at hand take place in the open forum of the
8 meeting. We are aware that members of the media
9 are anxious to speak with the FDA about these
10 proceedings. However, FDA will refrain from
11 discussing the details of this meeting with the
12 media until its conclusion. Also, the committee is
13 reminded to please refrain from discussing the
14 meeting topic during any breaks or lunch. Thank
15 you.

16 I'll now pass it on to Moon Hee Choi who
17 will read the Conflict of Interest Statement.

18 **Conflict of Interest Statement**

19 DR. CHOI: The Food and Drug Administration
20 is convening today's meeting of the Anesthetic and
21 Analgesic Drug Products Advisory Committee under
22 the authority of the Federal Advisory Committee Act

1 of 1972. With the exception of the industry
2 representative, all members and temporary voting
3 members of the committee are special government
4 employees or regular federal employees from other
5 agencies and are subject to federal conflict of
6 interest laws and regulations.

7 The following information on the status of
8 this committee's compliance with federal ethics and
9 conflict of interest laws, covered by but not
10 limited to those found at 18 USC Section 208, is
11 being provided to participants in today's meeting
12 and to the public. FDA has determined that members
13 and temporary voting members of this committee are
14 in compliance with federal ethics and conflict of
15 interest laws.

16 Under 18 USC Section 208, Congress has
17 authorized FDA to grant waivers to special
18 government employees and regular federal employees
19 who have potential financial conflicts when it is
20 determined that the agency's need for a special
21 government employee's services outweighs his or her
22 potential financial conflict of interest or when

1 the interest of a regular federal employee is not
2 so substantial as to be deemed likely to affect the
3 integrity of services which the government may
4 expect from the employee.

5 Related to the discussions of today's
6 meeting, members and temporary voting members of
7 this committee have been screened for potential
8 financial conflicts of interest of their own, as
9 well as those imputed to them, including those of
10 their spouses or minor children, and for purposes
11 of 18 USC Section 208, their employers. These
12 interests may include investments, consulting,
13 expert witness testimony, contracts, grants,
14 CRADAs, teaching, speaking, writing, patents and
15 royalties, and primary employment.

16 Today's agenda involves discussion of new
17 drug application NDA sufentanil sublingual tablets,
18 submitted by AcelRx Pharmaceuticals, Incorporated,
19 for the management of moderate to severe acute
20 pain, severe enough to require an opioid analgesic
21 and for which alternative treatments are inadequate
22 in adult patients in a medically supervised

1 setting. The committee will also be asked to
2 discuss risk-benefit considerations and whether
3 this product should be approved.

4 This is a particular matters meeting during
5 which specific matters related to AcelRx
6 Pharmaceuticals' NDA will be discussed. Based on
7 the agenda for today's meeting and all financial
8 interests reported by the committee members and
9 temporary voting members, no conflict of interest
10 waivers have been issued in connection with this
11 meeting.

12 To ensure transparency, we encourage all
13 standing committee members and temporary voting
14 members to disclose any public statements that they
15 have made concerning the product at issue. With
16 respect to FDA's invited industry representative,
17 we would like to disclose that Dr. William Herring
18 is participating in this meeting as a nonvoting
19 industry representative, acting on behalf of
20 regulated industry. Dr. Herring's role at this
21 meeting is to represent industry in general and not
22 any particular company. Dr. Herring is employed by

1 Merck and Company.

2 We would like to remind members and
3 temporary voting members that if the discussions
4 involve any other products or firms not already on
5 the agenda for which an FDA participant has a
6 personal imputed financial interest, the
7 participants need to exclude themselves from such
8 involvement, and their exclusion will be noted for
9 the record. FDA encourages all other participants
10 to advise the committee of any financial
11 relationships that they may have with the firm at
12 issue. Thank you.

13 DR. ZACHAROFF: Thank you. We will now
14 proceed with the FDA's introductory remarks from
15 Dr. Sharon Hertz.

16 **FDA Opening Remarks - Sharon Hertz**

17 DR. HERTZ: Good morning. Dr. Zacharoff,
18 members of the Anesthetic and Analgesic Drug
19 Products Advisory Committee and invited guests,
20 welcome. Today, we will be discussing a new drug
21 application for a novel sublingual sufentanil
22 formulation for the management of moderate to

1 severe acute pain in medically supervised settings.

2 Adequate control of acute pain after surgery
3 or painful procedures is important for helping
4 patients recover. Prescription opioids are often a
5 component of a multimodal analgesic approach, which
6 is standard in many institutions. However, the
7 treatment of acute pain must be balanced with
8 public health considerations related to abuse,
9 misuse, and accidental exposure.

10 The product at hand today is a drug device
11 combination. It contains 30 milligrams of the
12 Schedule II opioid agonist, sufentanil, and it is,
13 as I stated, for use in a medically supervised
14 setting. It's intended to be administered by a
15 healthcare provider to the patient sublingually
16 using a single-dose applicator is needed with
17 determined dosing intervals and a predetermined
18 maximum.

19 This is a 505(b)(2) application, and
20 sometimes there's confusion as to what that means.
21 A 505(b)(2) application means that the applicant is
22 relying in part on the agency's previous findings

1 of the efficacy and safety for another approved
2 product in, in this case for the injectable form of
3 sufentanil.

4 The objective for the program is not in fact
5 to decide whether sufentanil is an
6 analgesic -- that's already been determined -- but
7 whether the product is suitable for fulfilling the
8 indication; is it appropriate for treating the
9 population intended under the conditions that would
10 be labeled? This influences how much data are
11 necessary when we evaluate the product.

12 This application also relies on
13 cross-reference to safety data for another
14 sufentanil product, another formulation that was
15 evaluated in a different program. The efficacy and
16 safety of the product at hand was evaluated in one
17 placebo-controlled phase 3 trial in post-surgical
18 adult patients following abdominal surgery with
19 acute pain.

20 You're going to hear about the results of
21 this study and data from the 15-microgram related
22 product as well. Only one trial was required by us

1 to evaluate the efficacy of this product given
2 that, as I stated, sufentanil has already been well
3 characterized as an analgesic.

4 The safety profile of sufentanil sublingual
5 tablets, 30 micrograms, in acute pain was
6 consistent with the safety profile we would expect
7 of an opioid agonist, but there were two areas of
8 concern that required further evaluation: the
9 safety of this product when used at the maximal
10 proposed dose and the risk for misplaced tablets
11 due to the size of the product.

12 To address the safety of the 30-microgram
13 product in patients requiring the maximum dosing
14 proposed for labeling, the applicant reduced the
15 number from 24 to 12 in the current application and
16 provided new safety analyses. To address the
17 misplaced tablet potential, the applicant modified
18 the directions for use and performed additional
19 evaluations of the human factors that measure
20 whether or not instructions can be followed and are
21 reliable for those following them, the instructions
22 for use.

1 In this framework, there are several issues
2 we hope the committee will discuss today. These
3 include the efficacy of sufentanil sublingual
4 tablets, 30 micrograms, for acute pain; the safety
5 of this product with respect to the risks
6 associated with dropped and misplaced tablets; and
7 we're also going to be interested to hearing your
8 overall recommendation.

9 Thank you for your time and attention, and
10 I'm going to turn this back to Dr. Zacharoff.

11 DR. ZACHAROFF: Thank you.

12 Both the Food and Drug Administration and
13 the public believe in a transparent process for
14 information-gathering and decision-making. To
15 ensure such transparency at the advisory committee
16 meeting, FDA believes that it is important to
17 understand the context of an individual's
18 presentation.

19 For this reason, FDA encourages all
20 participants, including the applicant's nonemployee
21 presenters, to advise the committee of any
22 financial relationships they may have with the

1 applicant such as consulting fees, travel expenses,
2 honoraria, and interest in a sponsor, including
3 equity interests and those based upon the outcome
4 of this meeting.

5 Likewise, FDA encourages you at the
6 beginning of your presentation to advise the
7 committee if you do not have any such financial
8 relationships. If you choose not to address this
9 issue of financial relationships at the beginning
10 of your presentation, it will not preclude you from
11 speaking.

12 We will now proceed with AcetRx
13 Pharmaceuticals' presentations. Thank you.

14 **Applicant Presentation - Pamela Palmer**

15 DR. PALMER: Good morning. I'm Pamela
16 Palmer, cofounder and chief medical officer at
17 AcetRx. I'd like to thank the FDA and the
18 committee for your time and review of the data on
19 DSUVIA for the treatment of acute pain in a
20 medically supervised setting. I'm a board
21 certified anesthesiologist and directed the Pain
22 Management Center at the University of California

1 San Francisco, where for 15 years I emphasized
2 non-opioid analgesics for my patients, while
3 acknowledging that opioids are still required in
4 many clinical scenarios.

5 In my position at UCSF, I was asked to be an
6 expert witness on many wrongful death suits
7 involving in-hospital opioid dosing errors. In
8 many cases, the drug involved was injectable
9 morphine.

10 In 2005, the U.S. Pharmacopeia listed the
11 top 10 drugs with medication errors associated with
12 acute hospital care. The first drug was insulin
13 and the second drug was morphine. In this year,
14 AcclRx was founded in part to address this issue.
15 Unfortunately, according to the Institute for Safe
16 Medication Practices, opioids remain at the top of
17 the list with respect to medication errors.

18 It's not surprising that opioid medication
19 errors are so common. Commercially, morphine for
20 injection comes in 10 different dosage strengths,
21 from 0.5 to 50 milligrams per mL. Furthermore,
22 injectable opioids are clear solutions that all

1 look the same. They're easily substituted with
2 water or saline and frequently require documenting
3 of residual wastage. Despite these issues,
4 injectable opioids are currently the only way for
5 clinicians to rapidly treat moderate to severe pain
6 in many patients.

7 DSUVIA is a single-strength sublingual
8 tablet that avoids the issues associated with
9 injectable opioids and minimizes opioid dosing
10 errors. A sublingual formulation was chosen, as it
11 is a well known and well tolerated route that
12 provides rapid onset of action.

13 Currently, transmucosal opioids for
14 analgesia are only available for treatment of
15 opioid-tolerant patients with cancer or for chronic
16 pain. Avoiding the IV route of administration
17 aligns with the latest guidelines on postoperative
18 opioid pain management, which recommend oral over
19 IV opioids. Importantly, the sublingual route also
20 benefits patients with difficult IV access.

21 However, few opioids have the appropriate
22 physicochemical properties for effective sublingual

1 drug delivery. Therefore, it was important to
2 select a highly lipophilic opioid such as
3 sufentanil that allows for rapid mucosal
4 absorption.

5 Sufentanil is 1500 times more lipophilic
6 than morphine, and when dosed sublingually,
7 sufentanil provides more rapid analgesia than IV
8 morphine. This was demonstrated in a phase 3 study
9 conducted by AcelRx that compared sublingual
10 sufentanil to IV morphine.

11 Because sufentanil is potent, we're able to
12 use low-microgram dosing per tablet, allowing for a
13 small and well tolerated dosage form. During our
14 clinical development program, we determined the
15 minimum effective dose for DSUVIA as 30 micrograms,
16 which is dose equivalent to 5 milligrams of IV
17 morphine.

18 DSUVIA is immediate release and highly
19 bioavailable, therefore no excess drug loading per
20 tablet is necessary. DSUVIA also has no active
21 metabolites. DSUVIA was developed in collaboration
22 with the U.S. Department of Defense to provide a

1 noninvasive opioid analgesic that could be easily
2 administered in the field when rapid pain relief is
3 required.

4 A sublingual option has value for many
5 patients, including those with difficult to access
6 veins like those who are obese, the elderly, burn
7 patients, or those who are needle phobic, or when
8 oral medication is not optimal, such as patients
9 who have difficulty swallowing or NPO.

10 Early in development, it was determined that
11 the sufentanil sublingual tablet had to be small
12 and fast dissolving in order to be more tolerable
13 to patients being dosed as often as hourly and also
14 to maximize drug absorption. A DSUVIA
15 30-micrograms bioadhesive tablet takes an average
16 of 6 minutes to completely dissolve while fentanyl
17 lozenges may take up to 30 minutes.

18 Larger dosage forms like the fentanyl
19 lozenges also reflexively trigger the production of
20 saliva. The DSUVIA 3-millimeter diameter tablet
21 avoids this issue and provides consistent
22 pharmacokinetics by maximizing transmucosal

1 absorption of sufentanil and avoiding the
2 inadvertent swallowing of solubilized drug, which
3 for sufentanil would result in less than 10 percent
4 gastrointestinal bioavailability.

5 Finally, while the tablet is small, most
6 patients know they've been dosed with DSUVIA. Over
7 80 percent of subjects reported a taste following
8 dosing in our phase 1 study.

9 Other tablets such as sublingual
10 nitroglycerin or oral hydromorphone are similarly
11 small in diameter. However, these products are
12 dosed by hand and are available for use at home.
13 DSUVIA will be administered by a healthcare
14 professional, not the patient. A single-dose
15 applicator was developed to aid healthcare
16 professionals in safe and proper placement of the
17 sufentanil sublingual tablet.

18 DSUVIA distribution and administration will
19 be limited only to medically supervised settings,
20 and DSUVIA will not be available for use at home.
21 The applicator itself has additional built in
22 safety features. A single 30-microgram tablet is

1 prefilled and visible through the clear body of the
2 single-dose applicator. This allows a healthcare
3 professional to see when the tablet has been
4 dispensed.

5 There's a lock component that prevents
6 accidental dispensing of the tablet. Once the rock
7 is removed, the healthcare professional actuates
8 the green plunger to dispense the tablet. The
9 plunger is non retractable to clearly indicate when
10 an applicator has been used and to help mitigate
11 against refilling the applicator with a substitute
12 tablet.

13 Furthermore, each DSUVIA single-dose
14 applicator is contained in a sealed tamper-evident
15 pouch. The packaging must be torn open to access
16 the preloaded applicator. Each pouch is barcoded
17 to track dispensing electronically. Complete
18 illustrated fold-out directions for use are
19 attached to each pouch.

20 The proposed indication for DSUVIA is for
21 the management of moderate to severe acute pain,
22 severe enough to require an opioid and where

1 alternative treatments are inadequate. DSUVIA will
2 only be indicated for adult patients treated in a
3 medically supervised setting.

4 DSUVIA can be dosed by a healthcare
5 professional as needed for pain management with a
6 minimum of 1 hour between doses and a maximum of 12
7 tablets in 24 hours. A medically supervised
8 setting is defined as a DSUVIA REMS certified
9 licensed pharmacy or healthcare provider with DEA
10 registration for Schedule II drugs who must also
11 have access to equipment and who are trained to
12 manage opioid overdose. Additionally, AcelRx will
13 only certify facilities that have recent experience
14 administering IV opioids. This definition means
15 that no retail pharmacies will carry or dispense
16 DSUVIA.

17 In 2016, we submitted a 505(b)(2)
18 application for DSUVIA, which references the
19 extensive clinical experience of Sufenta, a
20 sufentanil citrate injection used as an IV
21 anesthetic, IV analgesic, and epidural analgesic
22 agent for over 30 years. The safety and efficacy

1 of sublingual sufentanil was evaluated in 10 phase
2 2 and phase 3 clinical trials, which were included
3 in the DSUVIA NDA. A total of 686 patients were
4 exposed to at least 30 micrograms of sublingual
5 sufentanil with most patients receiving multiple
6 doses throughout the studies.

7 In June of this year, we were approved
8 throughout the European Union. First, I'll give
9 more detail on the studies supporting the NDA.
10 These studies evaluated non-opioid tolerant
11 patients in medically supervised settings. The
12 efficacy and safety of DSUVIA 30 micrograms is
13 demonstrated in 4 clinical trials, 2 randomized
14 placebo-controlled studies in the postoperative
15 setting and 2 open-label safety studies, one in the
16 emergency department and one in the postoperative
17 setting.

18 The safety of DSUVIA is also supported by 6
19 Zalviso studies. The Zalviso patient-controlled
20 analgesia system dispenses sublingual sufentanil 15
21 micrograms tablets at the patient's request with a
22 20-minute lockout. This product is currently

1 approved in Europe and is in development in the
2 U.S.

3 In agreement with the FDA, patients from the
4 Zalviso studies are included in the DSUVIA safety
5 database based on their utilization of a
6 dose-equivalent or higher exposure. In 2017, we
7 received a complete response letter from the FDA.
8 The letter stated the FDA's concern with lack of
9 patient exposures at the proposed maximum daily
10 DSUVIA dose of 24 tablets per day.

11 The FDA also requested modifications to and
12 revalidation of our directions for use to mitigate
13 the risk of a drop tablet, which occurred 3 times
14 out of almost 1800 dispenses in our DSUVIA clinical
15 program. In response, we lowered our maximal daily
16 dose from 24 tablets to 12 tablets based on actual
17 usage in our clinical trials. We conducted new
18 safety analyses to support this new lower maximal
19 dosing. We also revised our directions for youth
20 and validated these changes in a human factors
21 study.

22 We agree with the FDA that the results of

1 this study support the safe and effective use of
2 this product by the intended users. In addition, a
3 consulting firm with risk analysis and child safety
4 expertise performed an assessment of accidental
5 DSUVIA exposure to vulnerable populations. With
6 use restricted to a medically supervised setting,
7 this analysis demonstrated that the risk due to a
8 drop tablet resulting in harm is very low.

9 Regarding our product-specific REMS, we
10 agree with the FDA's goal of mitigating the risk of
11 respiratory depression due to accidental exposure.
12 DSUVIA will be distributed only to REM certified
13 facilities following the attestation of an
14 authorized representative who must attest to
15 certain requirements, including the following:
16 first, the facility's ability to manage an opioid
17 overdose; second, that healthcare professionals
18 have read the directions for use prior to
19 administration of DSUVIA; and finally that DSUVIA
20 is only administered to patients in a medically
21 supervised setting.

22 In addition to the REMS attestation, AcelRx

1 will verify that sites seeking certification are
2 currently administering IV opioids in their
3 facilities. To detective aversion and suspicious
4 ordering, we will monitor the distribution supply
5 chain and audit wholesalers' data. We will also
6 audit certified healthcare facilities to evaluate
7 adherence to the REMS. And importantly, we will
8 decertify facilities that are noncompliant with the
9 REMS program.

10 With this background in mind, let me review
11 the agenda for the remainder of our presentation.

12 Dr. Jim Miner will discuss the unmet need.

13 Dr. Dennis Fisher will then present the clinical
14 pharmacology that differentiates DSUVIA from other
15 analgesic options. I will turn to present the
16 efficacy results from our clinical program, and
17 Dr. Neil Singla will follow with the safety
18 results. I will then return to review our
19 educational materials, REMS program, and conclude
20 the presentation.

21 We also have additional experts with us
22 today to help with your questions. All external

1 experts or their institutions have been compensated
2 for their time and travel.

3 Thank you. Now I'd like to invite Dr. Miner
4 to the lectern.

5 **Applicant Presentation - James Miner**

6 DR. MINER: Good morning. My name's Jim
7 Miner, and I'm the chief of emergency medicine at
8 Hennepin County Medical Center and the vice chair
9 of emergency medicine at the University of
10 Minnesota. I've been treating trauma and injury
11 patients for 20 years, usually in very severe pain.
12 I was also an investigator in the DSUVIA emergency
13 room study.

14 Today we're discussing the need for
15 analgesia in an acute medically supervised setting,
16 which cannot be effectively managed with a
17 non-opioid alternative. This is very different
18 from opioid products prescribed to patients in the
19 outpatient setting, which are frequently discussed
20 by this committee.

21 Let me be clear. I'm not advocating
22 expanding use of opioids. However, I know that

1 opioids sometimes are necessary and a sublingual
2 option would be an effective alternative to opioids
3 that are currently available. In fact, the joint
4 guidelines of the American Pain Association, the
5 American Society of Regional Anesthesia and Pain
6 Medicine, and the American Society of
7 Anesthesiologists continue to recommend opioids as
8 part of a multimodal approach to pain management.

9 Additionally, the American College of
10 Emergency Physicians, of which I'm a member,
11 supports the appropriate use of opioids for
12 treatment of new onset, moderate to severe acute
13 pain in adult patients presenting to the emergency
14 department. Appropriate, effective, and safe
15 management of moderate to severe pain is critical
16 for patients, and there are clear benefits of
17 effective acute pain management in a medically
18 supervised setting.

19 For example, in a study of more than 2,000
20 emergency department patients found that earlier
21 analgesic treatment led to earlier patient
22 discharge. Conversely, unrelieved post-op pain can

1 limit mobility, delay recovery, and prolong time to
2 discharge. If early acute pain is prolonged or
3 managed ineffectively, this can result in
4 psychological distress as well as the progression
5 to chronic pain.

6 A 2010 New England Journal article showed
7 that injured soldiers treated with opioids during
8 early resuscitation had less likelihood of
9 developing post-traumatic stress disorder than
10 soldiers not treated with opioids.

11 We tend to consider the IV route as optimal
12 for treating acute conditions, but this is not
13 always the case. Current IV opioids have
14 pharmacodynamic limitations. Morphine, even when
15 delivered IV, can have a slow and unpredictable
16 onset of action. Small analgesic doses of fentanyl
17 are often used initially to overcome the slow onset
18 of morphine, but fentanyl has a short duration of
19 action and requires frequent re-dosing. Dr. Palmer
20 mentioned opioid errors, and in the environment in
21 which I work, I have witnessed this.

22 Lastly, there are many challenges to

1 initiating IV access to administer an analgesic.
2 IV initiation is invasive and painful and result in
3 analgesic gaps from catheter infiltration for IV
4 tubing obstructions, and while infrequent, carries
5 risks such as infection for both the patient and
6 the healthcare professional.

7 IV access is time consuming and often
8 difficult to perform quickly. Many patients
9 presenting with acute, moderate, or severe pain
10 don't have an IV in place. The failure rate for
11 successfully placing an IV the first time is fairly
12 high. The first IV attempt fails in 12 to 26
13 percent of patients.

14 Important to why I'm here today, there are
15 many situations in which initiating IV access can
16 be quite challenging. For some patients, venous
17 access can be difficult and therefore time
18 consuming. When a patient is in severe pain, even
19 small delays result in prolonged suffering, which
20 you can imagine can be terrible from the patient's
21 perspective.

22 Imagine a patient arriving at the hospital

1 with severe pain after breaking their arm. The
2 pain has made the patient sweaty, and the
3 provider's struggling to place the IV. As the
4 poking for the IV continues, the pain goes
5 untreated and typically worsens as they become more
6 distressed by the ongoing pain and our attempts to
7 get an IV started.

8 Obesity is the main reason for difficult IV
9 access. There's also a fairly high rate of
10 needle-phobic patients, where attempting to start
11 an IV can cause significant anxiety. Venous access
12 is often difficult in the elderly and in burn
13 patients. In addition, there can be cases where IV
14 access is interrupted at a time when pain
15 management is still needed.

16 Denture muscular and oral routes also have
17 limitations. Intramuscular administration of
18 opioids is a painful route and is rarely used due
19 to the slow and unpredictable onset. Oral opioids
20 have a slow onset of action around 30 to 60
21 minutes. Also, there are some perioperative
22 patients who need to remain NPO, and there are many

1 patients who have difficulty swallowing pills for
2 various reasons, with approximately 15 percent of
3 the elderly population affected by dysphasia.

4 There are transmucosal fentanyl products
5 that have been developed for breakthrough pain
6 episodes in opioid-tolerant patients suffering from
7 cancer pain, but because of their high doses,
8 they're not suitable for opioid-naive patients.

9 While there is a general understanding that
10 opioids with active metabolites can be undesirable
11 in certain patients, this topic deserves more
12 discussion. Many opioids commonly used in the
13 clinical setting have active metabolites. Active
14 metabolites are mainly cleared by the kidneys,
15 which can be problematic in renally impaired
16 patients. Administering opioids with active
17 metabolites can also be problematic with respect to
18 titration and can result in delayed side effects,
19 making the safe treatment of pain relief more
20 difficult in the acute setting.

21 In conclusion, a non-IV option that works
22 quickly would address many of the challenges with

1 current opioid options, and it would be a great
2 advance in certain situations. For example, in
3 patients with severe pain who don't yet have an IV,
4 the sublingual route would allow us to relieve
5 their pain earlier in the patient's treatment.

6 This will be especially important in
7 trauma and burn patients during the initial minutes
8 of their treatments. Likewise, you can imagine a
9 scenario where the IV catheter's infiltrated; for
10 example, in a post-op setting during transport from
11 the operating room to the recovery room.

12 Finally, in patients presenting with
13 moderate or severe pain who require strong pain
14 medications but otherwise don't need an IV, such as
15 patients presenting with non-displaced fractures,
16 joint injuries, or local burns, the sublingual
17 route would allow us to circumvent the placement of
18 an IV and treat the patient more efficiently
19 without the need for a painful IV stick, making
20 their care less complicated and faster.

21 A product with a relatively rapid onset of
22 analgesia, no active metabolites, and given in a

1 monitored setting would be a welcome addition to
2 our pain management treatment options.

3 Thank you. Next, I'd like to invite
4 Dr. Fisher to the lectern.

5 **Applicant Presentation - Dennis Fisher**

6 DR. FISHER: Good morning. My name is
7 Dennis Fisher, and I will contrast the clinical
8 pharmacology of sublingual sufentanil to other
9 products. I'm an emeritus professor of anesthesia
10 at the University of California, San Francisco,
11 having spent 20 years on the faculty. At present,
12 I run a consulting company where I conduct
13 pharmacokinetic, pharmacodynamic, and
14 pharmacometric analyses for pharma companies.

15 The pharmacokinetic and pharmacodynamic data
16 that I will present suggest that DSUVIA, which
17 contains sufentanil, a lipophilic opioid, would be
18 expected to have a relatively rapid onset of
19 analgesia. Duration of analgesia should be longer
20 than that following IV administration of sufentanil
21 and should last several hours.

22 The 30-microgram dose has been selected to

1 maintain analgesia but minimize risk of side
2 effects. Several factors, including age, weight,
3 and inhibition of cytochrome P450, influence the
4 plasma concentration profile and could influence
5 the time interval at which patients need additional
6 doses. However, since the dosing interval for this
7 product is determined by the patient and the nurse
8 rather than at a fixed interval, the dosing
9 interval can be adjusted to maintain analgesia.

10 First, I'd like to discuss the results of
11 the single and multiple dose DSUVIA pharmacokinetic
12 study comparing it to 30 micrograms of intravenous
13 sufentanil. This study was conducted by AcelRx in
14 healthy subjects. The blue line is the mean of the
15 plasma concentration profiles from 40 subjects
16 following intravenous administration. The high
17 peak concentration puts the patients at risk for
18 ventilatory depression. The red line is the
19 hypothetical brain or effect site concentration.
20 This profile was simulated based on published EEG
21 models. Because sufentanil is so lipophilic, the
22 brain concentration tracks the plasma

1 concentration.

2 Finally, the green line at the bottom of the
3 panel, at 24 picograms per mL, is sufentanil's
4 analgesic threshold assessed in postoperative
5 patients. A single 30-microgram IV dose of
6 sufentanil can provide several hours of analgesia,
7 but at the expense of the potential for ventilatory
8 depression.

9 Now contrast the image from the previous
10 slide repeated here on the left to the
11 concentration profile with a smaller IV dose on the
12 right. It's important to note the difference in
13 the scales of the X and Y axes. The smaller dose
14 yields a markedly lower C_{max}, maximum plasma
15 concentration, and in turn, less likelihood of
16 ventilatory depression. But duration of analgesia
17 is brief, 30 minutes versus 3 hours.

18 Unfortunately, there's no IV dose of
19 sufentanil that yields both an acceptable C_{max} and
20 an intermediate duration of action. I note that
21 this is not unique to sufentanil. The same
22 limitation applies to other lipophilic opioids such

1 as fentanyl, which is why you heard from Dr. Miner
2 that small doses of intravenous fentanyl require
3 frequent re-dosing.

4 Now contrast this to the sublingual
5 administration of sufentanil in the DSUVIA product.
6 The left panel repeats the image for the
7 6-microgram IV dose. The right panel shows a
8 single 30-microgram sublingual DSUVIA dose. Again,
9 it's important to note the difference in the axes.

10 Sublingual administration has several
11 important effects. First, bioavailability is 50 to
12 60 percent, so area under the curve is smaller
13 compared to IV administration of a comparable dose.
14 Second, the absorption process dampens the rate of
15 rise and the peak concentration. Effect site
16 concentration peaks at one half of the value with
17 IV administration of the 6-microgram dose despite
18 the 30-microgram dose being much larger.

19 Third, although DSUVIA takes longer to reach
20 analgesic thresholds concentrations, approximately
21 15 to 30 minutes, the time spent above the
22 threshold for analgesia is markedly longer compared

1 to 6 micrograms IV. In fact, it's similar to the
2 duration of analgesia with 30 micrograms IV. Thus,
3 DSUVIA offers a good balance of onset and duration
4 while avoiding high-peak plasma concentrations.

5 One important consideration with repeated
6 administration of any drug is whether the washout
7 of drugs slows over time, which could result in an
8 unexpectedly long duration of action. To address
9 this, study 101 conducted by AcclRx compared the
10 time course of the single dose of DSUVIA, 30
11 micrograms, and 12 doses at intervals of 1 hour.

12 Here you see the plasma concentration of the
13 single dose in red and the final dose of the
14 multi-dose arm of that study in blue. Note that
15 this 1-hour dosing interval is similar to the time
16 that concentration peaks after a single dose. As a
17 result, repeated dosing at this interval leads to
18 accumulation, a doubling of the peak concentration
19 between the first and 12th doses.

20 In clinical practice, the actual dosing
21 interval is about 3 to 4 hours, therefore,
22 accumulation will be smaller in magnitude. This

1 accumulation allows healthcare professionals to
2 individualize treatment for patients who require
3 higher sufentanil concentrations.

4 The time-to-peak concentration following
5 both the first and 12th doses are similar,
6 occurring just before one hour. Of greater
7 importance is the time for the plasma concentration
8 to decrease by half after the peak concentration is
9 attained, shown by the red and blue arrows. As you
10 can see, it's similar approximately 2 and a half
11 hours after each of the first and 12th doses.
12 Therefore, the consistent decrease in concentration
13 should lead to predictable offset of effect
14 following single or multiple doses.

15 Various factors could influence the plasma
16 concentration profile of DSUVIA. Each of these has
17 been studied by AcclRx. Clearance increases
18 slightly with weight and decreases with age.
19 Hepatic and renal impairment yielded no effect on
20 clearance. The largest impact on the
21 pharmacokinetic characteristics of DSUVIA is
22 co-administration of an inhibitor of CYP3A4.

1 Ketoconazole increased Cmax of a single dose
2 by 19 percent and area under the curve by 77
3 percent. Each of these factors could influence
4 DSUVIA's clinical profile, however, clinically
5 DSUVIA is to be administered on an as-needed basis,
6 which will adjust for these effects in clearance. o

7 Now, we can contrast DSUVIA to morphine. As
8 Dr. Miner stated earlier, even after taking the
9 time to start an intravenous line, morphine, the
10 common opioid of choice, can have delayed and
11 erratic effects. The blue line on the graph shows
12 the plasma concentration following 2 doses of 3 and
13 a half milligrams of IV morphine dosed 30 minutes
14 apart. The red line represents the effect site or
15 brain concentration model from the EEG data.

16 As you can see, brain concentrations have
17 not even peaked at the time that the second dose is
18 administered. From a physiological perspective,
19 this is most likely explained by morphine being
20 markedly less lipophilic than sufentanil. This
21 resulted in morphine penetrating the blood-brain
22 barrier slowly. This delayed equilibration may not

1 only slow onset of analgesia, but also complicate
2 titration.

3 If intravenous morphine is slow on onset,
4 consider what happens when morphine is administered
5 orally. Not surprisingly, absorption delays the
6 pharmacokinetic profile and slows the onset of
7 analgesia compared to IV administration.

8 Therefore, the gastrointestinal route of absorption
9 with oral opioid medications may not be optimal for
10 patients requiring rapid relief from moderate to
11 severe pain, and oral morphine is unlikely to
12 result in a rapid onset of analgesia. In contrast,
13 DSUVIA can offer timely pain relief while avoiding
14 the IV route of administration.

15 Thank you. Next, I'll invite Dr. Palmer
16 back to the podium to discuss the efficacy results
17 of the DSUVIA clinical trials.

18 **Applicant Presentation - Pamela Palmer**

19 DR. PALMER: Thank you, Dr. Fisher.

20 Next, I'll present data supporting DSUVIA's
21 effectiveness and quickly reducing patients'
22 moderate to severe acute pain within 15 to 30

1 minutes. The selection of the 30-microgram dose
2 was based on our Zalviso studies where the median
3 usage in the first hour of more than 600 patients
4 was 30 micrograms.

5 We conducted a phase 2 study, study 202, to
6 confirm this dose selection and also provide
7 insight into efficacy in musculoskeletal pain in
8 patients following bunionectomy. A 20-microgram
9 dose was included to assure we were proceeding with
10 the lowest effective dose

11 Study 202 utilized an earlier tablet
12 formulation with a 9 percent lower systemic
13 exposure compared to DSUVIA's to-be-marketed
14 formulation. In agreement with the FDA, we omitted
15 this study from the safety analyses but will
16 present efficacy data to the committee.

17 Both studies 202 and our phase 3 study 301
18 were conducted in the U.S. and were randomized,
19 double-blind, placebo-controlled studies using
20 typical analgesic protocol design. These studies
21 included a total of 261 patients suffering from
22 moderate to severe acute pain over 12 to 48 hours.

1 This efficacy presentation will primarily
2 focus on these two studies with supporting evidence
3 of efficacy also coming from two additional
4 open-label DSUVIA studies. These additional
5 open-label, single-arm studies were conducted in a
6 total of 216 patients exposed to DSUVIA. Study 303
7 included patients who were 40 years or older with
8 an emphasis on enrolling patients with
9 comorbidities. Study 302 evaluated DSUVIA in 76
10 patients in the emergency department setting.

11 While DSUVIA will likely have clinical
12 utilization in a postoperative setting, which was
13 the patient population for the controlled studies,
14 demonstrating clinical utility in other settings
15 such as the emergency department is supportive of
16 an indication for management of moderate to severe
17 acute pain in the medically supervised setting.

18 All four clinical studies of DSUVIA utilized
19 a similar study design, only the patient population
20 and the dosing duration differing among the study.
21 Short-term studies from 5 to 48 hours were
22 conducted to reflect the likely settings of use for

1 DSUVIA such as emergency departments, outpatient
2 surgery, or other short exposure settings. Dosing
3 was at the patient's request, but no more
4 frequently than hourly, and pain intensity and pain
5 relief scores were recorded by the patient at 6
6 time points. Opioid rescue was available in all 4
7 studies to minimize early termination.

8 In the clinical studies, SPID, or summed
9 pain intensity difference, was used for multiple
10 endpoints. SPID is a cumulative measurement of
11 pain control over a period of time that allows for
12 analgesic efficacy to be compared between treatment
13 groups. The primary endpoint in our
14 placebo-controlled studies was SPID 12, which is
15 the summed pain intensity difference over 12 hours.
16 This is a commonly used endpoint for measuring
17 acute pain.

18 A key secondary endpoint included in the
19 studies was with SPID1, which is the sum of the
20 pain intensity difference in the first hour, which
21 for DSUVIA measures the efficacy of a single dose.

22 We also evaluated the onset of analgesia.

1 This was measured via a number of assessments. In
2 all the studies, even those without a comparator
3 group, we analyzed when pain intensity and pain
4 relief statistically separate from the baseline
5 pain intensity score or separate from zero in the
6 case of pain relief.

7 In the placebo-controlled studies, a second
8 analysis can be performed by comparing when the
9 active treatment group statistically separates from
10 placebo for pain intensity and pain relief score.
11 And lastly, in the 2 placebo controlled studies,
12 the double stopwatch technique was also used in
13 which the patient had to click the stopwatch when
14 they could detect analgesia and again when they
15 felt they had achieved meaningful analgesia.

16 Now, moving to patient demographics, the
17 patient demographics were generally balanced across
18 arms. Because of the interest from the Department
19 of Defense, we actively recruited males for an even
20 sex distribution in the bunionectomy study since
21 these studies are usually 85 to 90 percent female.

22 Patients mean age was in their early 40's.

1 Our study population had good representation across
2 different racial and ethnic groups. Approximately
3 one-third of the patients were obese, which is an
4 important safety subgroup because they can have
5 increased side effects with opioids, especially
6 after surgery.

7 101 patients in study 202 were randomized to
8 receive either placebo or 20 or 30 micrograms of
9 DSUVIA. 100 patients received study drug and
10 minimal early terminations for any reason occurred
11 during the 12-hour study period.

12 Based on the superiority of the 30-microgram
13 dose of DSUVIA in study 202, 163 patients in study
14 301 were randomized to receive DSUVIA 30 micrograms
15 or placebo. As mentioned, our analysis will focus
16 on the 30-microgram DSUVIA dose compared to
17 placebo.

18 Therefore, the 60 bunionectomy patients from
19 study 202 and the 161 abdominal surgery patients
20 from study 301 are included in our efficacy
21 analysis.

22 Now, turning to the primary endpoint

1 results, in both placebo-controlled studies, DSUVIA
2 30 micrograms provided statistically significant
3 efficacy in reducing patients moderate to severe
4 acute pain as demonstrated by the primary efficacy
5 endpoint of the difference between active and
6 placebo treatments in the SPID12.

7 This chart depicts a similar effect for each
8 study, which is the difference between to DSUVIA
9 and placebo SPID12 values and the standard error.
10 This supports the efficacy of DSUVIA 30 micrograms
11 in both musculoskeletal and soft tissue pain. In
12 contrast, the 20-microgram dose was insufficient.
13 Therefore, the remainder of the presentation will
14 focus on the 30-microgram dose.

15 We also evaluated efficacy across subgroups,
16 and the difference in SPID12 varied minimally by
17 demographics. In order to increase the power, we
18 pulled the results from DSUVIA studies 202 and 301.
19 Overall, DSUVIA is effective across subgroups.

20 The pain intensity over the first hour gives
21 you a clinical sense of the patient's initial
22 analgesic response to a single dose of DSUVIA

1 compared to placebo. Here we have graphed the pain
2 intensity at each 15-minute time point for
3 study 202. The 30-microgram dose achieved a
4 significantly greater pain reduction in the first
5 hour as measured by SPID1 compared to placebo with
6 a p-value of less than 0.001.

7 A similar pain intensity response in the
8 first hour is observed in study 301. DSUVIA had a
9 greater SPID1 compared to placebo with a p-value of
10 less than 0.001.

11 As mentioned earlier, three different
12 approaches can be used to measure analgesic onset:
13 the time to show a statistical difference from the
14 baseline pain score; the time to show a statistical
15 difference from the placebo group; and the double
16 stopwatch technique. Overall, DSUVIA demonstrated
17 rapid pain control within 15 minutes to 30 minutes
18 in both placebo-controlled studies.

19 Now let's look at the results from two
20 open-label studies. While SPID was used to
21 calculate efficacy in these studies, there was no
22 comparator arm to compare the values. Therefore,

1 in our open-label studies, we show you pain
2 intensity on the left and the pain relief data on
3 the right.

4 In study 303, onset of analgesia, as
5 measured by a statistical change from baseline,
6 occurred at 30 minutes for pain intensity and 15
7 minutes for pain relief. The pain intensity and
8 pain relief efficacy achieved by 2 hours was
9 maintained throughout the rest of the study.

10 Similar results were observed in study 302,
11 our emergency department study where patients came
12 in with an average baseline pain intensity score of
13 8.1. Following a single dose of DSUVIA, a drop
14 from baseline in pain intensity and an increase in
15 pain relief compared to baseline was evident at 15
16 minutes and continued to improve over the first
17 hour. At 60 minutes after a single dose, a 35
18 percent reduction in pain intensity was evident.

19 Next, I'll explain how we arrived at our
20 proposed maximal daily dose. As I mentioned
21 earlier, we are proposing a reduced daily dose of
22 12 tablets based on our clinical trial utilization.

1 This bar graph shows the number of tablets taken by
2 patients ranging from 1 to 15 DSUVIA tablets over
3 24 hours.

4 Although dosing with DSUVIA is allowed as
5 frequently as every hour, you can see from this
6 graph that far fewer than 24 doses were required to
7 maintain analgesia over 24 hours. In fact, the
8 average inter-dosing interval over the 24-hour
9 period was 3.7 hours, consistent with the PK
10 profile showed earlier by Dr. Fischer. Since
11 92 percent of patients use 12 tablets or less per
12 day, this is our recommended daily limit.

13 This limit is also consistent with
14 real-world treatment, as physicians tell us that if
15 a patient requires dosing every hour for an
16 extended period of time, they should be switched to
17 an alternate method of analgesia, as this high
18 frequency of dosing becomes impractical.

19 In summary, we agree with the FDA that the
20 primary and secondary analyses support the efficacy
21 of DSUVIA for the management of moderate to severe
22 acute pain. A large inconsistent effect was

1 established in both musculoskeletal and soft tissue
2 acute pain compared to placebo, and efficacy in the
3 emergency department patients was similar to that
4 observed in the postoperative patients.

5 The onset of analgesia was rapid for a
6 noninvasive analgesic on average within 15 minutes
7 or at the latest by 30 minutes, depending on the
8 study and the method of assessment. This onset is
9 not surprising after observing the plasma
10 concentrations following the single dose of DSUVIA
11 in a PK study.

12 Finally, while patients with higher
13 analgesic requirements can be dosed as often as
14 hourly, the average patient required dosing every 3
15 to 4 hours over the course of a day. Therefore,
16 while DSUVIA is a single-strength tablet to avoid
17 dosing errors, the flexibility in timing of
18 re-dosing allows healthcare providers to
19 individually titrate to a patient's unique
20 analgesic needs.

21 Thank you. Next, Dr. Singla will present
22 the safety results.

1 **Applicant Presentation - Neil Singla**

2 DR. SINGLA: Thank you, Dr. Palmer.

3 My name is Neil Singla. I'm an
4 anesthesiologist and the founder and chief
5 scientific officer of Lotus Clinical Research. I
6 participated in DSUVIA clinical trials as a
7 principal investigator. Sufentanil with its
8 decades of use has a well characterized safety
9 profile. Today, I'll present the data showing that
10 the DSUVIA safety profile is broadly consistent
11 with other opioids used in medically supervised
12 settings.

13 The DSUVIA safety database consists of three
14 patient pools. The overall safety population is
15 comprised of all DSUVIA and Zalviso phase 2/3
16 studies, excluding study 202 at the request of the
17 FDA, because it used an earlier tablet formulation.
18 These clinical trials include uncontrolled as well
19 as active- and placebo-controlled trials and range
20 from 5 to 72 hours in duration.

21 The next pool consists of only
22 placebo-controlled studies to get an accurate

1 comparative safety profile of DSUVIA. For this
2 reason, it was limited to the first 24-hour period
3 because less than 2 percent of DSUVIA adverse
4 events occurred beyond this period.

5 To further evaluate the safety of DSUVIA,
6 adverse event data was analyzed comparing higher-
7 and lower-dosing patients from all studies of at
8 least 24-hours duration, which we are calling
9 pool 8, with adverse events evaluated for up to 72
10 hours of exposure. First, I would like to explain
11 why certain Zalviso patients are included in the
12 DSUVIA safety database.

13 The inclusion of Zalviso patients in the
14 DSUVIA safety database was agreed upon with the FDA
15 because a PK study demonstrated that 2 doses of
16 Zalviso 15 micrograms dosed 20 minutes apart were
17 equivalent to a single 30-microgram dose of DSUVIA.

18 As you can see, the PK curves displayed here
19 show that the concentration profiles were quite
20 similar. The bioequivalence criteria were met for
21 both AUC and Cmax. Based on these PK results, 323
22 Zalviso patients who administered their second dose

1 within 20 to 25 minutes of the first dose were
2 included in the DSUVIA safety database.

3 In support of the DSUVIA NDA, 10 phase 2 and
4 phase 3 clinical trials were performed. As noted,
5 I will focus on those studies that had a placebo
6 arm to provide a relevant comparison of safety.
7 Therefore, the 318 patients who received DSUVIA or
8 Zalviso and the 158 placebo patients are used for
9 the following analyses.

10 When compared to placebo, the overall safety
11 profile for sufentanil was consistent with that of
12 acute opioid treatment. Sixty-seven percent of
13 patients experienced at least one adverse event,
14 and the most common adverse events were nausea,
15 headache, and vomiting. The adverse event rates
16 were similar to or slightly higher for active
17 versus placebo.

18 Overall, there were few patients with
19 adverse events leading to discontinuation. Four
20 percent of patients in both the active and placebo
21 treatment groups discontinued treatment. All
22 events leading to discontinuation occurred at rates

1 less than 1 percent, and the most common reason was
2 nausea.

3 Next, I would like to review serious adverse
4 events in the placebo-controlled studies. There
5 were no SAEs with DSUVIA in the placebo-controlled
6 studies. Four serious adverse events occurred in
7 2 sufentanil patients from the Zalviso studies.
8 One patient experienced decreased oxygen
9 saturation, and the second patient experienced a
10 pulmonary embolism, which lead to hypoxia and
11 confusion.

12 Additionally, 2 placebo patients in the
13 DSUVIA study experienced SAEs, one with syncope and
14 the other hemiparesis. There were no deaths in the
15 DSUVIA studies. There was 1 death in a patient
16 treated with Zalviso. This was a 69-year-old woman
17 who was randomized to receive Zalviso and died of
18 acute renal failure 30 days after her last dose of
19 Zalviso. This event was considered unrelated to
20 treatment by the study investigator.

21 Let's now take a closer look at safety
22 topics of special interest: respiratory events, a

1 comparison of adverse events at high and low
2 exposure, and the human factors study. Overall,
3 discontinuations due to respiratory events were
4 infrequent in both the active- and
5 placebo-treatment groups. Although infrequent,
6 based on the known risk of respiratory depression
7 with opioids, warnings and precautions related to
8 the risk of respiratory depression have been
9 included in the proposed labeling for DSUVIA.

10 Moving to the safety profile of comparing
11 patients who used higher and lower dosing, as
12 mentioned, the proposed label for DSUVIA
13 30-milligram tablet will be up to 12 tablets in a
14 24-hour period.

15 This limitation was not based on any
16 observed safety signal, however, as the FDA
17 requested analysis of safety following the maximal
18 proposed daily dose, the adverse event data for
19 patients dosing greater than versus less than 300
20 micrograms for a 24-hour period are compared for up
21 to 72 hours. These data are presented from pool 8
22 consisting of clinical trials with a duration of at

1 least 24 hours.

2 Here is an overview of the safety profile
3 for sufentanil comparing patients receiving a daily
4 dose of less than 300 micrograms to those receiving
5 300 micrograms or more. There is no apparent dose
6 response for severe adverse events, serious adverse
7 events, or adverse events leading to
8 discontinuation.

9 Regarding typical opioid adverse events,
10 there was a slight dose-dependent increase in
11 nausea and pruritis in the higher dosing group.
12 For the remaining adverse events, there was not a
13 consistent dose-dependent increase.

14 There was also additional safety information
15 from the commercial experience with Zalviso in
16 Europe. Zalviso has been available in Europe for a
17 little over 2 years to treat moderate to severe
18 acute pain in postoperative patients. A review of
19 the pharmacovigilance data collected from April
20 2016 to June 30, 2018 shows an adverse event
21 profile similar to the DSUVIA and Zalviso clinical
22 trial data. These real-world data of Zalviso

1 provide further support to the safe use of
2 sufentanil tablets.

3 Overall, the DSUVIA and Zalviso safety data
4 set aligns with the well characterized safety
5 profile of sufentanil that has been collected over
6 the last 30 years. In agreement with the FDA, the
7 safety profile is consistent with other opioids
8 that are used in a medically supervised setting.

9 Since few patients required more than 12
10 tablets, the proposed label will be with a maximum
11 of 360 micrograms or 12 tablets in a 24-hour
12 period. The safety profile is similar between
13 patients receiving less than 300 micrograms and
14 patients receiving 300 micrograms or more in 24
15 hours, and the FDA agrees that the analyses support
16 the maximal daily dose proposed.

17 To address the risk of a dropped tablet,
18 AcelRx conducted a human factor study. Dropped
19 tablets were rare in the clinical trials, and in
20 each of the three cases, the tablet was recovered
21 and accounted for. Importantly, these occurrences
22 were prior to the improvements to the directions

1 for use.

2 The goals of the human factor study were to
3 validate the revised directions for use, assess if
4 healthcare professionals could properly administer
5 DSUVIA, and confirm placement of the tablet to
6 mitigate the risk of a dropped tablet. In
7 agreement with the FDA, changes were made to the
8 directions for use and were assessed in the human
9 factor study, and emphasis was placed on the
10 handling of the single-dose applicator to prevent
11 accidental actuation as well as confirmation of
12 tablet placement in the patient's mouth.

13 Modifications were made to the illustrations
14 of the mouth anatomy to allow for greater clarity
15 of tablet placement. Instructions were added on
16 what steps to take if a tablet is not in the
17 patient's mouth after the plunger was actuated,
18 including locating and disposing of the tablet.
19 Additionally, the directions for use were attached
20 to each DSUVIA package.

21 The human factor study demonstrated that
22 healthcare professionals can successfully

1 administer DSUVIA in accordance with the directions
2 for use, which includes confirming proper tablet
3 placement. All 45 participants successfully
4 administered a placebo tablet using the single-dose
5 applicator and confirmed placement in the mouth of
6 3 mock patients. Importantly, there were no
7 dropped tablets.

8 Based on the data from this study, the FDA
9 Division of Medication Error Prevention and
10 Analysis determined that the product-user interface
11 supports the safe and effective use of the product.

12 Thank you. Dr. Palmer will now return to
13 conclude the presentation.

14 **Applicant Presentation - Pamela Palmer**

15 DR. PALMER: Thank you Dr. Singla.

16 Prior to summarizing our presentation, I'd
17 like to provide additional information on our
18 educational materials and REMS program. We will
19 have multiple approaches to providing educational
20 materials to healthcare professionals. In order to
21 emphasize the proper administration and
22 confirmation of tablet placement, we will attach

1 the directions for use to each single-dose pouch.
2 In addition, we will provide access to
3 instructional video, a safe-use guide, and placebo
4 devices for in-service training. We also have a
5 24-hour product support line and REMS website for
6 healthcare professionals.

7 Our approach to risk management is
8 three-pronged. Before a product is even
9 distributed, AcclRx will ensure sites have been
10 REMS certified via attestation by an authorized
11 representative. Before any product is
12 administered, healthcare professionals will have
13 been trained on the directions for use to emphasize
14 proper administration and confirmation of tablet
15 placement.

16 Finally, we will continue to monitor
17 facilities with real-time review of product
18 complaints and our pharmacovigilance data. We will
19 conduct regular supply-chain audits and use the
20 RADARS system to collect data on accidental
21 exposure, abuse, misuse, or diversion of DSUVIA.

22 In summary, DSUVIA's sublingual

1 administration provides a unique alternative for
2 effective acute pain relief that aligns with the
3 proven efficacy and safety established by
4 sufentanil. DSUVIA has a rapid plasma-brain
5 equilibration and provides an alternative to IV and
6 oral opioid medications in patients in a medically
7 supervised setting. DSUVIA has a predictable onset
8 of action of 15 to 30 minutes without the delay of
9 starting an IV. The 24-hour average re-dosing
10 interval was 3.7 hours, and DSUVIA does not have
11 any active metabolites.

12 Importantly, the safety and efficacy of
13 DSUVIA in non-opioid tolerant patients was
14 demonstrated across the clinical program to support
15 its use in moderate to severe acute pain, and
16 DSUVIA was also shown to be well tolerated with a
17 safety profile similar to other opioids.

18 With our educational and REMS programs in
19 place and by limiting DSUVIA to medically
20 supervised settings where it will be administered
21 by trained healthcare providers, we believe the
22 benefits of DSUVIA outweigh the risks. Thank you

1 for your time and attention, and I look forward to
2 answering your questions.

3 **Clarifying Questions**

4 DR. ZACHAROFF: Thank you.

5 We will now entertain clarifying questions
6 to the applicant. Are there any clarifying
7 questions for AcelRx? Dr. Meisel?

8 DR. MEISEL: Thank you. Steve Meisel with
9 Fairview; a few questions here. In studies 202 and
10 301, you said the average age, as I recall, was in
11 the low 40's. How many patients were over the age
12 of 65?

13 DR. PALMER: There were only a couple, and
14 in fact, that's why we went on and ran study 303,
15 was to add those additional patients.

16 DR. MEISEL: So how many patients total in
17 everything that you've reported today are over the
18 age of 65?

19 DR. PALMER: Let me show you that data right
20 there. With DSUVIA, we have 11 percent of the
21 patients over 65, and in Zalviso, 51 percent,
22 actually. So half of Zalviso patients were over

1 65. If you look combined in what we call our
2 overall safety population of 646 patients,
3 one-third of them are over the age of 65.

4 DR. MEISEL: But for efficacy, it's far
5 smaller. Correct? You only used Zalviso for the
6 safety, not for the efficacy.

7 DR. PALMER: Exactly. We used them for the
8 safety. I do have data on efficacy in the elderly
9 for the study 303, if you'd like to see that.

10 DR. MEISEL: I would. I'll give you a
11 minute to pull that up. In the mean time, about
12 absorption, I know that this is designed for people
13 with dry mouth and so forth, so there's not a lot
14 of swallowing. But there are people who are
15 naturally heavy saliva producers.

16 Have you assessed the impact of
17 bioavailability with patients who may be heavy
18 saliva producers?

19 DR. PALMER: Well, in the case of the dry
20 mouth that you mentioned first, we did allow ice
21 chips. And in fact, in our proposed label, we
22 recommend ice chips for excessively dry mouth. For

1 someone with excessive amounts of saliva, it is
2 possible they could solubilize and swallow more
3 drug, and therefore would require more frequent
4 dosing.

5 DR. MEISEL: On slide 17, one of the REMS
6 elements says that healthcare professionals have
7 read the directions for use, and there's going to
8 be an attestation of that. How would you propose
9 to an organization like mine, that might have 5
10 [000] or 6,000 nurses that come and go on a daily
11 basis, have read the directions, that can attest
12 that they've all read the directions for use?

13 DR. PALMER: We've actually talked to
14 healthcare providers and nurses, and they say that
15 actually when they are onboard or come in, or when
16 there are new products, that they frequently now
17 have electronic ways to measure the fact that
18 they've had in-services on various products, and
19 that we will be auditing that documentation. They
20 must document, and we will be auditing that they
21 have in fact been trained on the use of DSUVIA.

22 DR. MEISEL: So you're suggesting that every

1 single nurse -- and also attest that every single
2 nurse in the organization has been trained on this
3 prior to their using it?

4 DR. PALMER: For the ones that will be using
5 it, yes. That's what we are looking for.

6 DR. MEISEL: Okay. The last question I've
7 got -- while you put up the last slide -- on slide
8 number 3 -- I'm sorry, slide number 6, you said the
9 equivalent dose of 30 is 5 of morphine. H did you
10 come up with that?

11 DR. PALMER: We actually came up with that
12 in our active comparator studies for Zalviso. It
13 was called IEP 309. What we looked at in fact
14 was -- and we can switch to the next slide of
15 study 309's data. So we compared Zalviso, and we
16 let patients dose 15 micrograms with a 20-minute
17 lockout versus IV PC and morphine, where they had
18 1 milligram with a 6-minute lockout.

19 We actually looked at their dosing over the
20 first 5 hours of treatment, and what we saw was
21 that while they were using 90 micrograms of
22 sublingual sufentanil, they were using

1 15 milligrams of IV morphine. So we were comparing
2 those. And these were the same patient
3 populations, same types of surgery, so we really
4 found that that was -- from a human utilization
5 standpoint, DSUVIA 30 micrograms would equal
6 5 milligrams of IV morphine.

7 DR. MEISEL: But it sounded like you gave
8 half patients 5 milligrams of IV plus morphine and
9 half patients 30 of this product in, and you did
10 some comparative studies. This is sort of
11 inference.

12 DR. PALMER: Yes. It was looking at 200
13 patients in each group, around, and then looking at
14 how these patients both utilized the drug.

15 DR. MEISEL: Because I'm a little -- I find
16 that inference sort of hard to accept because in
17 your efficacy studies, when you threw out the 20-
18 microgram dose, it's because of lack of efficacy.
19 But if that's equivalent to 3 milligrams of IV
20 morphine, heck, that's higher than our normal
21 post-op starting dose, which is 1 to 2. And the
22 equivalent here, based on your arithmetic, is 3,

1 and you threw it out because it didn't work.

2 So the notion that 30 is 5, I guess I'd like
3 to see some harder data before I would make that
4 conclusion.

5 DR. PALMER: And you're right. You're
6 absolutely right. It's a rough estimate to give
7 providers. It's a unique drug. It's sufentanil
8 sublingual, so when you're trying to compare it to
9 a non-lipophilic drug via a different route, the
10 best thing we had was our active comparator data.
11 But you're absolutely right. It is a unique
12 product, and we're trying to give healthcare
13 professionals the general sense of what it is
14 equivalent to, but it is difficult to say exactly
15 what it's equivalent to, given it's a unique
16 opioid.

17 DR. MEISEL: You were going to pull up that
18 other data While we're --

19 DR. PALMER: Yes. I'd like to see
20 slide PE-3 regarding age and efficacy. And again,
21 we conducted 303 because we really found out after
22 conducting 202 and 301, which was mainly in an

1 ambulatory surgery setting, that we really didn't
2 have enough patients over 65. So we conducted
3 study 303 here, and you can see the breakdown for
4 the different age, gender, race, and BMI, and then
5 the SPID12, which was a primary endpoint. And
6 we're really not seeing much of a difference based
7 on age.

8 If you want to go to slide AL-8, in our
9 emergency room study, we also had elderly. Let me
10 put that up there. This is study 302, so this is
11 our emergency room study. Because it was short
12 duration, the primary endpoint was actually SPID1.
13 So you can see here, again, based on demographics,
14 we've got age, gender, race, and BMI. And we've
15 got very consistent SPID1, and that's the efficacy
16 of a single dose.

17 DR. MEISEL: Okay. Thank you. If my memory
18 is right, it's a total of 27 patients over the age
19 of 65, in those two studies.

20 DR. PALMER: Yes.

21 DR. MEISEL: Okay. Thank you.

22 DR. ZACHAROFF: Dr. Higgins?

1 DR. HIGGINS: I too am focused on the age
2 issue. The target population is the elderly,
3 specifically, so I'm very interested in talking a
4 little bit more about the AEs for that population.
5 I'd like to know a bit about the older adult
6 experience with DSUVIA. I'm looking at the
7 background material provided by the FDA, and I see
8 that on page 29, one of the SAEs was related to
9 hypoxia with a 65-year-old white female. The dose
10 that this individual had taken was 14 doses, which
11 is awfully close to the near recommended daily
12 dose, and we know that the clearance decreases with
13 age.

14 I guess I'm curious to know also, in
15 addition to about the overall experience of the
16 older adults involved in the studies, what were the
17 discontinuation ages, if you have that as well?
18 And finally, will DSUVIA be able to be used in
19 SNFs, skilled nursing facilities?

20 DR. PALMER: Okay. I'll break those down.
21 I'd like to show the -- let me show you here. This
22 is our DSUVIA data of adverse events based on age,

1 and this is DSUVIA only. I can also show you to
2 DSUVIA and Zalviso, if you're interested.

3 What we're seeing here is very consistent
4 with opioids after surgery in the elderly, so we
5 know as anesthesiologists that as a patient ages,
6 they're at more risk for various adverse events
7 afterwards, and that's very similar to the data
8 that we're seeing here.

9 So you see the CNS side effects of dizziness
10 and somnolence increasing. You also see the oxygen
11 saturation decreased adverse event increasing. By
12 the way, the advanced elderly patient there, there
13 are 8 advanced elderly that we treated with DSUVIA
14 that's over the age of 75. That's actually the
15 same patient who had somnolence and oxygen
16 saturation decreased.

17 It was a 75-year-old woman who was in the
18 emergency room, and her room air saturation was 97
19 percent. And with a dose of DSUVIA, it dropped
20 after about 30 minutes to 94 percent. So they gave
21 her some supplemental oxygen, and she was fine. So
22 she had a mild somnolence and mild oxygen

1 saturation decrease. But if you look at this
2 trend, this is very consistent with opioids in the
3 postoperative setting, and we believe that these
4 are very consistent, both from a trend with age as
5 well as the overall incidence.

6 Regarding the SAE you brought up of that
7 patient who is 65 years of age, yes, that was the
8 Zalviso patient. And I'd like to comment, Zalviso
9 is a 15-microgram with a 20-minute lockout PCA, so
10 they can actually use up to 45 micrograms in an
11 hour. So the exposure is much higher than you're
12 actually seeing with DSUVIA.

13 This was a post operative patient. They had
14 excessive use of opioids concurrently along with
15 DSUVIA. In fact, it was a site deviation because
16 the site was using actually more than we were
17 allowing of rescue medication.

18 The FDA brought that up in the briefing
19 book. That's what you see happen occasionally with
20 opioids after surgery; the patient received some
21 naloxone and was monitored and did fine. But we
22 are using opioids in an environment where you have

1 to make sure you monitor these patients.

2 You did ask a question around skilled
3 nursing facilities, and right now, we have no plan
4 to have any use in skilled nursing facilities.
5 We're only planning on where IV are currently used
6 and certainly our settings of use where we studied
7 it during our studies.

8 DR. HIGGINS: Thank you.

9 DR. ZACHAROFF: Dr. Warholak?

10 DR. WARHOLAK: So my questions are for
11 Dr. Palmer. On slide 78, it's indicated that
12 people will receive training.

13 DR. ZACHAROFF: Move to the mic closer.

14 DR. WARHOLAK: Okay. On slide 78, it's
15 indicated that people will receive direction for
16 use training. Can you tell us a little bit more
17 about that?

18 DR. PALMER: Yes. We are going to make
19 available placebo single-dose applicators and also
20 in-service training to any hospital that requires
21 it, or requests it I should say. Often hospitals
22 like to perform their own training, in which case

1 we will have the training materials available for
2 them. But the key thing is that they document the
3 training because we will be auditing for that.

4 DR. WARHOLAK: My next question is, can you
5 tell us how many patients received the total 12
6 doses in the studies?

7 DR. PALMER: Yes. If we could pull up some
8 data on the dosing, we had 9 patients in study 301
9 that went beyond that dose. This is DSUVIA dosing.
10 Check that. I'd like DSUVIA dosing. I might have
11 to get that to you after the break.

12 The average tablet utilization in study 301
13 was 7 tablets; 92 percent of people used 12 or
14 fewer tablets. But the exact number who
15 used -- your question exactly was the number who
16 used 12, exactly?

17 DR. WARHOLAK: Yes. Thank you.

18 DR. KAYE: It's slide 54.

19 DR. PALMER: There is the breakdown of the
20 histogram of the distribution for that 24-hour
21 study.

22 DR. WARHOLAK: Thank you. Then finally, on

1 slides 52 and 53, it indicates the analyses were
2 not adjusted for multiplicity. Can you tell us why
3 you decided to do that?

4 DR. PALMER: Sure. Yu-Kun Chiang, do you
5 want to discuss why these -- was the question why
6 they weren't?

7 DR. WARHOLAK: Yes.

8 DR. PALMER: Would you like to talk about
9 the statistical analysis?

10 DR. CHIANG: My name is Yu-Kun Chiang. I'm
11 the statistical consultant to AcelRx. This is an
12 open-label study, single arm, so basically we just
13 do a descriptive summary to compare to the
14 baseline, so what the changes are, an old
15 prespecified [indiscernible] comparison for this.
16 This indicates the trend and the magnitude of
17 changes.

18 DR. ZACHAROFF: Dr. Litman?

19 DR. LITMAN: Thank you. Ron Litman. I have
20 a few questions please, Dr. Palmer. Can you just
21 review for us, again, the exact definition of a
22 medically supervised environment setting?

1 DR. PALMER: Yes, go ahead and bring up that
2 slide. Thank you. It's a REMS certified licensed
3 pharmacy or healthcare provider with DEA CII drug
4 registration. And also the key thing is to have
5 the equipment to manage an opioid overdose as well
6 as the personnel.

7 We are actually adding an additional that's
8 not currently in the REMS proposed by us or by the
9 FDA and absolutely no interest in this drug being
10 used anywhere where IV opioids are not currently
11 used. So therefore, we can easily access a Synteny
12 database and make sure that any site that we're
13 REMS certifying in fact has been ordering and
14 receiving IV opioids.

15 DR. LITMAN: What about a patient that -- I
16 don't know; I'm going to make something up
17 here -- comes into the emergency room with kidney
18 stones. So it's not life threatening, but they're
19 in the waiting room. Can they get this in the
20 waiting room?

21 DR. PALMER: Actually, I'll have Dr. Miner
22 address that since he's the emergency room expert

1 here.

2 DR. LITMAN: I'm trying to get at what kind
3 of monitoring do you need to administer this?

4 DR. MINER: Jim Miner from Hennepin County
5 Medical Center. That's a really good question. I
6 envision this struggle only being used in the same
7 situation would use an IV opioid, so you'd have to
8 have the same monitoring use. I don't see it being
9 given in a waiting room, for example.

10 DR. LITMAN: So the medically supervised
11 setting, that the definition doesn't include
12 monitors.

13 DR. MINER: I guess I'm speaking for my
14 emergency department, how we'd run it. We
15 generally, if we're going to give an IV opioid, get
16 some sort of monitoring on a patient. The triage
17 systems have changed a lot in the last few years
18 for most emergency departments. Most patients see
19 a physician much earlier than they used to and get
20 triaged much earlier to different aspects of a
21 waiting room. We have a doc at our front desk that
22 meets people as they come in now, which is

1 different than it used to be, to try to sort out
2 people who need interventions, that need more
3 monitoring earlier in their care than we used to.

4 DR. LITMAN: So it sounds like it's possible
5 it could be in a waiting room if you had the
6 facilities to monitor or put in an IV. I'm just
7 trying to think of other uses. The most important
8 one I can think of would probably be an ambulance,
9 but it sounds like that would not qualify then as a
10 medically supervised setting in the definition
11 because they wouldn't be -- I guess have a REMS
12 certified pharmacy. Is that correct?

13 DR. PALMER: Well, that's a good point that
14 you bring up. We are interested only in settings
15 where IV opioids are used. We have not
16 studied -- we've studied only in hospitals,
17 ambulatory surgery centers, and emergency rooms.
18 We have not conducted studies in ambulances.

19 Paramedics were part of our human factor
20 study, but really that is an interesting question
21 for you all to discuss and opine on today, is if an
22 ambulance, for example, if the paramedics are

1 currently using IV opioids, is that in fact a safe
2 use for DSUVIA? We have not studied it there, and
3 it would be an interesting topic of discussion.

4 DR. LITMAN: And along the same lines, a
5 battlefield where IV opioids are used. They can't
6 be REMS certified, I would imagine based on your
7 definition, but it seemed like it would be an ideal
8 setting for this.

9 DR. PALMER: Well, the Department of
10 Defense, our supply to them is via their hospitals.
11 So as far as where we're distributing, it would be
12 going to a military hospital, and that would
13 qualify under the REMS. And we have been notified
14 by the Department of Defense that they will be
15 following our REMS.

16 DR. LITMAN: The second question I had is
17 you had mentioned in the presentation that the EU
18 has already approved a couple of different
19 versions, the Dzuveo and the Zalviso. How long
20 have they been in use in the European Union?

21 DR. PALMER: Well, Zalviso was approved in
22 2015. It was commercialized in 2016, so a little

1 over two years. The data we gave you of the 26,000
2 patients was back in June. We actually have about
3 30,000 patients. Again, that's 15 micrograms with
4 a 20-minute lockout. So 30,000 patients are
5 actually on average dosing, between 30 and 40 doses
6 during their stay. Dzuveo, which was just recently
7 approved is not commercialized yet.

8 DR. PALMER: I would assume then that the
9 European Union pharmaceutical safety regulatory
10 agencies have safety data that the FDA could use to
11 determine safety overall.

12 DR. PALMER: Yes, and we get those reports
13 as well, and we're just really thrilled with what
14 we're seeing there with those about 30,000 patients
15 at this point.

16 DR. LITMAN: My last question is actually to
17 Dr. Dart because I know you've told us about RADARS
18 in the past at several different meetings. Could
19 you just walk us through how you would envision
20 this product being monitored by the RADARS? I'm
21 not an expert on RADARS. I've heard about it from
22 you, but it seems like you would have to be

1 interviewing patients who are addicted, who have
2 gotten their hands on this.

3 Could you tell us theoretically how that
4 would work?

5 DR. DART: That's a good pickup. It's true.
6 Normally when RADARS does postmarketing
7 surveillance, we're looking at large numbers in the
8 outpatient community, so you pick those up when
9 they come into our various systems, which I can
10 explain if the committee would like, but that takes
11 a few minutes.

12 But basically we have -- RADARS, just very
13 quickly, is comprised of multiple programs that
14 have national coverage, including things like
15 poison centers; drug diversion investigators who
16 report what drugs they detect on the street; and
17 treatment programs that you refer to where people
18 tell us what they abused when they come in for
19 treatment for substance-use disorder.

20 So if you take all those systems together,
21 it provides what's called mosaic surveillance,
22 meaning surveillance from many different

1 directions. And we do that on drugs like
2 oxycodones, hydrocodones, et cetera, where you have
3 lots of exposure in the community, and then you
4 simply count the number of people who say, "I
5 abused hydrocodone," when they come in for
6 treatment, or they call the poison center, or a
7 drug diversion investigator detected that when they
8 arrested somebody.

9 So this is totally different, and it's a
10 great aspect of this drug because it won't escape
11 the medically supervised setting. So that's
12 community goes away, which means we're doing
13 something different here. We have to look -- even
14 one case in the case of DSUVIA would be of interest
15 to us, whereas one case of oxycodone is one out of
16 thousands usually.

17 So what we would do with RADARS in this case
18 is go to the programs that allow us to drill down
19 on that information. For example, a poison center
20 collects a lot of information about every call, and
21 poison centers actually get calls from healthcare
22 facilities regularly, and we do get calls on

1 dropped pills.

2 Now, I have to say that all the dropped pill
3 cases I've ever had were in the home where this
4 product won't be. I've never had one from a
5 healthcare facility, but it would be reasonable for
6 them to call us because they do that now.

7 So poison centers would be one way of
8 detecting that. We would also look at drug
9 diversion because if there is a single recorded
10 sale on the street, or arrest I should say on the
11 street, of DSUVIA, we'd want to know where that
12 happened. Because of their system, you'll be able
13 to look at that geographic region and say, well
14 what hospitals in that area actually have that drug
15 available?

16 So I can go on to my other systems. For
17 example, in drug treatment programs, if someone
18 reports abuse of DSUVIA, we'll want to know how
19 they got it, where they got it, et cetera. This is
20 the first time we've used RADARS this way, but we
21 think that it has a lot of potential to do that.

22 DR. LITMAN: Thanks very much.

1 DR. HERTZ: This is Sharon Hertz. Can I
2 just make a quick correction? We don't have some
3 magic access to European data. It has to come
4 through the sponsor.

5 DR. LITMAN: Got it. Thank you.

6 DR. ZACHAROFF: Mr. O'Brien?

7 MR. O'BRIEN: Yes, thank you. I just have a
8 couple of clarifying questions. For Dr. Palmer
9 first, if we could go back to -- I had the same
10 question, actually, that was already posed with
11 slide 13 with regard to first responders and
12 ambulances. So I think you answered that in the
13 sense that this wasn't intended to cover that.

14 I would just add -- and it would probably be
15 for a later discussion -- I don't see it applying
16 for my spine fusion surgeries, but clearly when I
17 had my small bowel obstruction and was taken out in
18 the ambulance and they couldn't get an IV in, I
19 would have greatly appreciated having DSUVIA at
20 that point in time, for sure, in that question.

21 I think the answer to the question at the
22 moment, we're not talking about first responders

1 and ambulances to have access to DSUVIA. Is that
2 correct?

3 DR. PALMER: We've not studied it in that
4 environment. Again, our human factors did have
5 paramedics participate, but we did not study that
6 environment, and that would be a topic of
7 discussion, I can imagine.

8 MR. O'BRIEN: Okay. Well, with regard to
9 what you did study, in slides 49 and 50, in terms
10 of the patient population for both bunionectomy and
11 abdominal surgery, does this actually represent who
12 you would expect to be the population for DSUVIA?

13 DR. PALMER: Well, these are key ways of
14 determining that a medication is effective for both
15 musculoskeletal and visceral pain. These are both
16 ambulatory surgery type operations where they're
17 done in a short-term environment.

18 We do see DSUVIA as being used as this sort
19 of transitional opioid. We don't see people
20 getting a steady diet of DSUVIA over days in the
21 hospital. We really see its advantages sort of
22 niche, if you will, in that setting of transition.

1 If you're coming out of the operating room,
2 you had an IV, it infiltrates, you're in severe
3 pain, they need to get another IV started, they can
4 give some DSUVIA; emergency room, you're coming in,
5 you don't have an IV at all, in significant pain,
6 and as Dr. Miner said, transitioning to an IV or in
7 fact just having 1 or 2 doses, and then being
8 discharged. So yes, these do support the use in
9 ambulatory surgery.

10 MR. O'BRIEN: So it would be a small slice
11 of the population of these two groups, actually,
12 that would have it.

13 With regard to that, again, in terms of the
14 LS mean here, I noticed in the slide that you just
15 had up for Dr. Meisel in response to that, there
16 seemed to be a much -- for that group, there seemed
17 to be a much larger reduction on the LS mean on
18 that. I think it went from 8 to 2 on that
19 particular slide, if I recall. I don't remember
20 the slide number. It was in response to the
21 question that Dr. Meisel has asked with over 65, I
22 think it was in a question.

1 I was just curious. Is that what we see as
2 this reduction -- I know it's statistically
3 significant, but going down, in essence, 1 or 1 and
4 a half on a pain score? Is that my interpretation
5 of that slide, going back to 49 and 50?

6 DR. PALMER: Yes. This is over the first
7 hour. And we know from the published literature
8 for both postoperative, Dan Carr's group, as well
9 as in the emergency room setting by Polly Bjur,
10 that they've looked at the NRS 0 to 10 scale and
11 determined that a drop of 1.3 is actually
12 clinically significant. And we know also from our
13 double stopwatch and our statistical onset data,
14 that patients are definitely feeling analgesia in
15 that first hour. And the emergency room I think is
16 quite dramatic with a 3-point drop when these
17 patients are coming in right off the street.

18 MR. O'BRIEN: On slide 54, just curious, it
19 might be just because it was another study, with
20 regard to determining the maximal dose, if I
21 recall -- I couldn't find it in the background.
22 But when I read it in the background, I think there

1 was one individual that had 77 doses during the day
2 or during the 24-hour period.

3 Do I recall that correctly or is it a
4 different study than the 301?

5 DR. PALMER: That could have been Zalviso,
6 and that could have been over multiple days. The
7 maximum anyone got in DSUVIA, in all of our trials,
8 was 15 tablets, and you see that was 2 patients
9 right there in slide CO-54. There are 2 patients
10 who got 15. That's the maximum anyone received of
11 DSUVIA in a 24-hour period.

12 MR. O'BRIEN: Thank you. I just had one
13 other clarifying question for Dr. Milner [sic] on
14 slide 28. In these scenarios, Dr. Milner, I'd be
15 curious to know what would be -- if there's any
16 data to show for these three scenarios, what we're
17 talking about in terms of the percentage of the
18 population that would actually benefit within these
19 particular groups in these scenarios.

20 Do you have any idea what it would actually
21 represent in terms of percentage of population that
22 could benefit by DSUVIA, particularly like scenario

1 3 that now would not have to require an IV that
2 typically would get an IV?

3 DR. PALMER: Dr. Miner?

4 DR. MINER: Thank you. I don't have data
5 that could represent accurately the whole country.
6 I can speak for my emergency department. In
7 scenario 3, patients with moderate to severe pain
8 who only are getting IV access for IV pain
9 medicines, it's a fairly common occurrence,
10 especially in long-bone fractures and burns, which
11 typically don't require IV medications other than
12 pain medications. But there really aren't any pain
13 medications that work orally that can be titrated
14 effectively in an emergency setting for somebody in
15 really severe acute pain but with no other
16 problems.

17 So I would say a typical emergency
18 department sees 200 patients a day, and there
19 probably would be 20 to 30 patients who would fall
20 into that scenario. Scenario 1, patients who are
21 severely hurt and don't have an IV placed yet, it
22 would be more dramatic that they would need pain

1 medicine right away. But that probably happens
2 more like 2 to 3 times a day where somebody comes
3 in with major trauma or burns and is going to get
4 an IV either way but is in such severe pain that
5 getting a pain medicine while the IV placement is
6 going on may be of benefit to them.

7 MR. O'BRIEN: For scenario 2, do we have any
8 data that shows what the percentage of infiltrated
9 catheters are, IV catheters?

10 DR. MINER: I don't.

11 MR. O'BRIEN: No? Okay. All right. Thank
12 you very much. That's all.

13 DR. ZACHAROFF: Hi. Kevin Zacharoff, and I
14 have some questions myself.

15 Dr. Miner, if you would, I just want to be
16 clear about the fact that we're considering, from a
17 clinical perspective, that there is no titration
18 capability with this medication. Is that correct?

19 DR. MINER: Yes. You could give a second
20 dose an hour later.

21 DR. ZACHAROFF: So if I give somebody a dose
22 and in 10 minutes they're still in pain, then as a

1 clinician, what would I do?

2 DR. MINER: Work on starting an IV.

3 DR. ZACHAROFF: Okay. And I would work on
4 Starting an IV with the intention of giving them
5 other opiates. Is that correct?

6 DR. MINER: Yes.

7 DR. ZACHAROFF: Okay. Thank you. So my
8 question would be, is there any data that's
9 available to show patients who received a
10 sublingual tablet, who then got opioids in less
11 than an hour?

12 DR. PALMER: Yes. In fact, not only did
13 these patients have opioids coming from the
14 operating room for all of our postoperative
15 studies, but we did allow opioid rescue analgesia.

16 If you could actually pull up this slide of
17 the Kaplan-Meier time to first rescue. We'll be
18 pulling that up. You can see here in study 301, of
19 the folks that did use rescue, you can see here
20 that much of it was in that first hour. And that
21 really gets to the point of titration. Once they
22 have that first dose, yes, they are fixed there for

1 60 minutes. But following that, they actually have
2 quite an ability to titrate to different plasma
3 levels, depending on their individual need.

4 DR. ZACHAROFF: What medication was used for
5 rescue?

6 DR. PALMER: This was IV morphine.

7 DR. ZACHAROFF: And do you have any data
8 about amounts of morphine that were administered?

9 DR. PALMER: Yes. If we could get the
10 rescue slide for that study 301? The use of rescue
11 for study 301 was fairly low. If you look, in
12 general, study 301 compared to placebo was low use.

13 If we could actually get the data where it's
14 the percent of people who had rescue and then their
15 actual dose that they received? So the percentage
16 of patients who had rescue in the different
17 studies -- here you go. In study 301, it's 27
18 percent of patients in the DSUVIA arm. And again,
19 like I told you, the majority of those were early
20 on, and then 65 percent in placebo.

21 For the actual dose that they received of
22 rescue, of those who received rescue --

1 DR. ZACHAROFF: So in study 202 --

2 DR. PALMER: -- it was about 2 milligrams of
3 morphine.

4 DR. ZACHAROFF: So in study 202, 70 percent
5 of patients?

6 DR. PALMER: Here you go. Sorry. Study 301
7 here, of the patients who received rescue in
8 study 301, you can see in the active group that the
9 mean use was 2 milligrams of IV morphine and the
10 placebo group is 3.3.

11 DR. ZACHAROFF: Okay. And just from a
12 safety perspective, is there anything that's being
13 proposed in your materials that identifies patients
14 who have received this medication, like typically
15 patients who have a PCA might have a band on their
16 wrist or some type of delineating characteristic,
17 or is the only thing that exists is notation in the
18 medical record?

19 DR. PALMER: Yes. As far as this
20 nurse-administered opioid, it's not as though
21 there's any identification that the patient has
22 received it. As an anesthesiologist, I was very

1 careful to make sure that we really evaluated this
2 in the settings that would be used.

3 I know that, for example, in a bunionectomy,
4 a lot of the times people will start those studies
5 on post-op day 1. We started our study immediately
6 after they came out of the operating room. We
7 really tried to make sure that the concomitant
8 medications are getting in the OR, the drugs are
9 getting in the OR. We did not limit the opioids
10 that they could receive in the operating room or
11 the PACU leading into our use of DSUVIA. We wanted
12 to make sure we were looking at real-world
13 scenarios. We didn't have any limits on BMI. We
14 had no limits on age.

15 So I feel as an anesthesiologist quite
16 comfortable with how we studied this drug.

17 DR. ZACHAROFF: Okay. Is there anything in
18 your materials, your REMS materials -- you
19 mentioned disposal in the event that the tablet is
20 dropped. Is there anything specifically about how
21 disposal takes place, whether it needs to be
22 witnessed, how it's disposed?

1 DR. PALMER: Actually, standard operating
2 procedures in hospitals will absolutely mandate all
3 CII has to be witnessed and has to go in special
4 CII disposal.

5 DR. ZACHAROFF: Okay. Then just lastly, the
6 whole idea of a medically supervised setting, a
7 REMS certified pharmacy is mentioned. If I
8 understood the definition of a medically supervised
9 setting, I heard everything you said about a
10 hospital setting, it seems like this will be used
11 in a hospital setting.

12 But let's assume that we approve it, and it
13 can be used in a REMS certified pharmacy. Does
14 that mean there needs to be oxygen available if the
15 patient desaturates? Does that mean there needs to
16 be a provision to start an intravenous on the
17 patient in the event that they need to be
18 administered naloxone?

19 DR. PALMER: Our original REMS actually
20 mandated that supplemental oxygen naloxone would be
21 available on those sites. That exact wording, we
22 could certainly have a conversation with the FDA

1 regarding the exact terminology in that REMS. I
2 would like to see that.

3 DR. ZACHAROFF: But it could be possible in
4 a REMS certified pharmacy that a patient might
5 receive repeated doses an hour apart of this
6 medication, if I understand.

7 DR. PALMER: The pharmacy's really for
8 shipment and where they're supplying within their
9 hospital or their ambulatory surgery center. The
10 key thing there is that those folks have the
11 ability to manage. And that's why it's so
12 important to make sure that we're cross-referencing
13 and these sites are actively using IV opioids.
14 That makes me have a sense of security that these
15 folks know how to handle an opioid overdose.

16 DR. ZACHAROFF: Okay. So then based on what
17 you just said, my understanding is that a REMS
18 certified pharmacy would act as a distributor but
19 not as an administer.

20 DR. PALMER: Yes.

21 DR. ZACHAROFF: Okay. Thank you.

22 Dr. Terman?

1 DR. TERMAN: Yes. Thank you. I have a
2 couple of practical questions, which may or may not
3 be helpful to anybody but me, And then one about
4 the data?

5 First, Dr. Miner, patients come into the
6 emergency room in severe pain, how easy is it to
7 get them to cooperate with the sublingual
8 administration device?

9 DR. MINER: That's a great question. I've
10 only administered this during the trial for
11 patients who are in moderate to severe pain, but
12 moderate to severe pain enough where they can
13 consent for a trial, so not the truly most severe
14 pain patients.

15 Generally speaking, when somebody's in
16 severe pain, they're very eager to get pain relief
17 and cooperative as can be, and their mouths are
18 generally open. So I don't see that being a
19 challenge to getting this medicine to a patient.

20 DR. TERMAN: Okay. Good. Thank you.

21 Dr. Palmer, I wasn't reading the material
22 before I got here. I didn't know there was a

1 bioadhesive on the tablet. That innovative. Does
2 that affect someone trying to swallow the tablet if
3 it was found on the ground, for instance? Do you
4 think it would be difficult to actually swallow it?
5 I mean, it turns out it's not very effective as
6 it's swallowed, but do you think the bioadhesive
7 would keep it from going down?

8 DR. PALMER: Well, I could have Larry Hamel
9 discuss exactly what the bioadhesive is. We have
10 done swallowing studies, so if someone wanted to
11 swallow this, you just take a glass of water and
12 you can swallow it down. So the bioadhesive
13 doesn't stop it.

14 When it's placed sublingually, it's
15 basically a hydrogel. So it takes a few seconds to
16 imbibe some saliva, and then it creates sort of a
17 hydrogel patch in the sublingual space. But if one
18 were to put this in their mouth and then swallow
19 water -- we had to do those studies, actually.
20 That's why we know we only have 9 percent
21 bioavailability from the gut.

22 DR. TERMAN: Let me ask about slide 51. I'm

1 very interested in the time of onset. If you can
2 get a sublingual fast time of onset -- as mentioned
3 both in what you've talked about and some of the
4 online opinions that were put in on this docket, I
5 think you've got something if it's fast, but what
6 I'm not sure is how fast it is.

7 Can you tell me -- you didn't mention it in
8 this, but you did mention that you also looked at
9 both perceptible analgesia and meaningful
10 analgesia. And according to the information that I
11 have in the preconference material, it seemed like
12 the meaningful analgesia was even longer than 30
13 minutes.

14 Could you talk about that?

15 DR. PALMER: Absolutely. Here is study 301,
16 perceptible and meaningful there. The double
17 stopwatch is interesting. If you've even noticed
18 that the perceptible at 24 minutes for that study
19 was quite lagging behind the 15 minutes where the
20 pain intensity was differing from baseline -- well,
21 first of all, I'd like to say that 15 minutes is
22 the first time we measured any pain intensity or

1 pain relief, so it could have been that someone had
2 an onset earlier.

3 I find the double stopwatch technique, to be
4 honest with you, a little bit flawed because in
5 these studies, you're handing these patients these
6 stop stopwatches. They're straight out of surgery.
7 They've got somebody asking them every 15 minutes
8 what is your pain intensity, what's your pain
9 relief, what's your pain intensity, what's your
10 pain relief? And you can't remind them about the
11 stopwatches, so you're kind of relying on them
12 remembering, oh that's right, I'm supposed to hit
13 this one with receptive and on this one with
14 meaningful.

15 So while I realize, it tends to be the gold
16 standard of care, I think it is fraught with
17 difficulty and probably often lags the true onset
18 of analgesia from what I've seen.

19 DR. TERMAN: Okay. I think that's all.
20 Thank you.

21 DR. PALMER: Sure.

22 DR. ZACHAROFF: Ms. Willacy, did you have a

1 question? Please identify yourself, and then speak
2 into the mic.

3 MS. WILLACY: I'm Jacqueline Willacy. Based
4 on the nursing aspect of it, in a
5 critical -- postoperative, you have a patient come
6 from the OR. Do these patients have to be in a
7 monitored bed or can they be on a regular floor?
8 And being on the regular floor, the nurse-patient
9 ratio a lot of times poses a problem in monitoring
10 these patients.

11 So how do we go about looking into it, as
12 far as the nursing, to take that aspect away from
13 it in terms of monitoring the patients?

14 DR. PALMER: Yes, absolutely. Again, we
15 studied these patients both in DSUVIA and Zalviso,
16 where they were on a regular floor. And especially
17 with Zalviso because we were studying them out to
18 3 days after major surgery, so they certainly
19 weren't on any sort of step-down or ICU level care.

20 When opioids are being given to a patient,
21 usually pulse oximetry, continuous pulse oximetry,
22 is commonly there. But we don't really see this as

1 any different than any other nurse-administered
2 analgesic, whether it's one-on-one nursing in a
3 PACU or in fact if it's on the floor where they
4 have PRN dosing. But we do recommend -- our draft
5 label certainly suggests that continuous monitoring
6 for respiratory depression is important, for these
7 patients and any patient receiving an opioid.

8 MS. WILLACY: Well, in the real-world of
9 nursing on the floor, you don't have continuous
10 pulse ox. It's typically in a controlled
11 environment where that happens. Post-operative,
12 you go to a surgical post, surgical floor. There's
13 no pulse ox. It's probably Q4 hours. My take on
14 it, the patient has to be continuously monitored
15 pulse ox.

16 My other question is our elderly population,
17 in terms of they can't metabolize the medication to
18 a certain -- they get delirious, especially when it
19 comes to night. So I'm wondering if there's any
20 area of study -- I have not gone through the entire
21 material -- to see how that will affect our elderly
22 population.

1 DR. PALMER: I'm sorry. Can you clarify the
2 last part of your question?

3 MS. WILLACY: Our elderly population; we
4 have elderly patients.

5 DR. PALMER: Yes.

6 MS. WILLACY: And some of the opioids do
7 create a problem for them in terms of getting
8 delirious. So I'm wondering if there's any
9 area -- if you guys have done any study for the
10 elderly population to see how that will not create
11 a problem.

12 DR. PALMER: Yes. I think when I was
13 showing earlier that based on age, we did see an
14 increase in CNS -- we're talking about dizziness,
15 somnolence -- as well as an oxygen saturation
16 decrease, which again is very common. You're
17 absolutely right, very common with the elderly
18 after surgery and opioids. We didn't see it beyond
19 what we would normally expect for an opioid.

20 But interestingly, we actually did -- you
21 mentioned this. We don't have this in our briefing
22 book, and I apologize for that, but in our

1 emergency room study, we actually conducted a
2 cognitive assessment where we looked at patients
3 before dosing and an hour after dosing. It's
4 called the six-item screener, and the Department of
5 Defense requested this because they actually want
6 to know that if a soldier needs to be dosed with
7 this -- they were worried, with ketamine sometimes
8 they can have dissociative effects. They wanted to
9 know if there was any cognitive impairment with
10 DSUVIA.

11 In fact, here are the results from our
12 six-item screener. It's very simple. You ask
13 about the year, the month, and the day, and then
14 you give them three items to remember, and then an
15 hour later you ask them the same questions. What
16 we actually had is of the 76 emergency room
17 patients, 75 of them answered the questions both
18 before and after, recruited in the analysis. And
19 you can see here that of the bullets on the bottom,
20 73 patients either had the same score, in fact, an
21 increase in their score, so they improved on the
22 exam, and only 2 patients only had a 1-point

1 decrease.

2 I think that even speaks to -- and it's a
3 little bit off the subject of what was asked, but
4 when patients are in pain, they have difficulty
5 answering questions and being cooperative, and then
6 after a dose of DSUVIA, actually some of them
7 improved. So I thought that was interesting. But
8 from an elderly standpoint, we are an opioid. And
9 you're absolutely right; you have to watch the
10 elderly more carefully.

11 DR. ZACHAROFF: We are running over, but
12 we're going to give you a few more minutes to ask
13 some brief questions. Dr. Fischer?

14 DR. FISCHER: Thanks. I'll be very quick.
15 Mike Fischer from Boston. We had some discussion
16 early on about the potential importance of this
17 agent for opioid-naive patients. What's the
18 experience in terms of either efficacy or safety
19 with patients who are not opioid naive, either in
20 your trials or especially in the real-world use
21 data that you've been accumulating from Europe?

22 DR. PALMER: And just to clarify for the

1 committee, we describe folks as non-opioid
2 tolerant. The FDA, according to the labels,
3 describe opioid tolerant as 60-milligram oral
4 morphine equivalent or more per day. What we
5 describe as non-opioid tolerant is they could have
6 been opiate naive all the way up to taking 15
7 milligrams of oral morphine equivalent. We wanted
8 to be real world. There are the people who are
9 taking an occasional Vicodin here or there, you
10 can't technically call them opiate naive, but they
11 certainly are not opioid tolerant.

12 So we excluded anyone taking more than 1-
13 milligram oral morphine equivalent, which is about
14 3 Vicodin a day. In our draft label, we have
15 language stating that if you're planning on using
16 it in someone who's taking more, you have to
17 monitor carefully for inadequate analgesia. This
18 dose may not be enough for them, and they really
19 possibly should use something else.

20 DR. FISCHER: Are there any data from Europe
21 that speak to how that's working out in real-world
22 settings where presumably plenty of those patients

1 are on baseline opioids?

2 DR. PALMER: Yes. We've not received data
3 specifically that categorizes them as an opioid
4 tolerant and how they've done, but that would be an
5 interesting postmarket study.

6 DR. ZACHAROFF: Ms. Phillips?

7 MS. SHAW PHILLIPS: Quick question that
8 follows up on Dr. Litman and Ms. Willacy's related
9 to the REMS adherence and the difference between a
10 medically supervised setting and medically
11 supervised -- but when you're talking about
12 auditing the healthcare facilities, is that only
13 just to follow up on their documentation of
14 training, or is it really to look at what patient
15 populations are using it in, how they're
16 supervising it, whether they have good control, or
17 whether their usage numbers are in line with how
18 they say they're using it, and so on?

19 DR. PALMER: Terrific. I'd like to show you
20 that. Our REMS audit plan, in fact, we're planning
21 on auditing a hundred percent of the initial users
22 to assess compliance with the REMS, and that

1 involves a number of things: the REMS training
2 records for the healthcare professionals
3 administering DSUVIA, so, again, they need a
4 document that they have trained these folks who are
5 using DSUVIA.

6 Any reports of dropped tablets; we want to
7 see the patterns of use within the facility to make
8 sure that in fact it's not going to a pediatric
9 ward, and we can't wait to start those studies. We
10 think there's a great need in the pediatrics, but
11 we have not conducted them now. We do not want
12 DSUVIA used in that patient population now; any DEA
13 Form 106's that have been filed.

14 Also, we're going to be looking at the
15 automated dispensing cabinet wastage records. This
16 is a single-dose, fully-administered product. If
17 there's any wastage of it, it might be because, for
18 example, a tablet was dropped and they had to waste
19 it. So we really want to carefully look at that to
20 make sure that there's not any problems with
21 excessive wastage and how they're using it.

22 Then moving forward beyond the initial

1 users, we will be looking at a statistically
2 verified sampling of sites, and we'll have that
3 discussion with the FDA on what percentage of sites
4 we'll be auditing moving forward.

5 DR. ZACHAROFF: Okay. Last question,
6 Dr. Kaye.

7 DR. KAYE: Question for Dr. Palmer. I was
8 interested in timing and varied onset of opiates in
9 the presented studies, and I was happy to see a low
10 incidence of naloxone use. My question was, with
11 the rescued population where morphine was given,
12 would you characterize it as equal, or similar, or
13 relatively low compared with the group where it was
14 used without the morphine or the rescue?

15 DR. PALMER: So those receiving rescue
16 versus not, and what specific endpoint were you --

17 DR. KAYE: I was just saying, in general,
18 would you say it was similar or equally as low as
19 those who did not need a rescue with morphine?

20 DR. PALMER: Similar? Low? I'm sorry.
21 What was low? What parameter was low?

22 DR. KAYE: The use of naloxone.

1 DR. PALMER: Oh, sorry, the use of naloxone.
2 Sorry. There was no use of naloxone in any DSUVIA
3 patient. There were 3 Zalviso patients that
4 required naloxone, and then there were 2 -- in
5 fact, let me put that slide up so you can see that.
6 No DSUVIA patient required naloxone; 3 Zalviso
7 patients and then 2 placebo patients.

8 DR. KAYE: Thank you very much.

9 DR. PALMER: Yes. Sorry for
10 misunderstanding that.

11 DR. ZACHAROFF: Dr. Meisel, we can give you
12 2 minutes.

13 DR. MEISEL I'll be very quick. On
14 slide 54, you say that almost everybody -- well, it
15 says here, 3.7 hours was the average dosing
16 interval. And on slide 33, it looks like the
17 duration of action is about 3 hours with a 1-hour
18 peak.

19 Why did you pick Q1 hour as a dosing
20 frequency as opposed to, say, Q2 or Q3? Because
21 you also know that it builds up, and your slide 34
22 shows that you have an accumulation effect.

1 DR. PALMER: Yes. Accumulation is actually
2 intentional for this; otherwise you literally are
3 having a one-size-fits-all situation. So by
4 allowing the re-dosing interval to be right after
5 the peak effect -- I'm sorry. The peak effect
6 occurred before the previous dose, you know that
7 the patient has experienced the maximal effect, and
8 you know that it's not effective enough. So both
9 the nurse and the patient then can make that
10 decision to have a second dose.

11 Accumulation allows you, in fact, to then
12 get to a higher plasma level. We know from our
13 DSUVIA studies -- in fact, I'd like to see the
14 different doses with the different plasma levels.
15 Sometimes people say to us, "How could one size fit
16 all? You've got this single dose." But by
17 allowing this inter-dosing interval, you're
18 actually allowing people to be quite flexible with
19 the different doses.

20 So if you've got patients who can -- well,
21 this is an average. There's actually the
22 inter-dosing interval slide where people can dose

1 different doses and achieve different concentration
2 levels.

3 On average, DSUVIA patients dosed to about a
4 40 to 50 picogram per mL concentration, and the
5 Zalviso patients, there were more major surgeries,
6 and they used it for longer. They actually more to
7 about 70 to 100 picograms per mL. But the
8 flexibility, really, with DSUVIA is that you can
9 use a little every 4 to 6 hours, or you can in fact
10 use it every hour for a period of time to get up to
11 what you need and then maintain your dosing.

12 DR. ZACHAROFF: Thank you. We will now take
13 a 15-minute break. Panel members, I'm just going
14 to remind you, please remember there should be no
15 discussion of the meeting topic during the break
16 amongst yourselves or any other member of the
17 audience. We will resume promptly at 10:30. Thank
18 you.

19 (Whereupon, at 10:14 a.m., a recess was
20 taken)

21 DR. ZACHAROFF: Welcome back. We will now
22 proceed with the FDA presentations.

FDA Presentation - Ning Hu

1
2 DR. HU: Good morning. My name is Ning Hu.
3 I'm a clinical reviewer in the Division of
4 Anesthesia, Analgesia, and Addiction Products. I'm
5 also a practicing physician. This morning, I will
6 be providing an introduction and the clinical
7 review of safety and efficacy for the new drug
8 application or NDA 209128, for sufentanil
9 sublingual, 30-microgram tablet.

10 Here's an overview of FDA's presentations
11 today. I will start with an introduction and
12 review of clinical safety and efficacy, then
13 Dr. Townsend will present the human factors
14 evaluation, and Dr. LaShaun Washington-Batts will
15 present the risk evaluation and mitigation
16 strategies or REMS. I will then end with the
17 overall benefit-risk considerations.

18 Here's the outline of my presentation this
19 morning, first, the introduction. Sufentanil
20 sublingual 30-microgram tablet has a proposed trade
21 name of DSUVIA. Sufentanil is a Schedule II opioid
22 analgesic. The sufentanil sublingual tablet is

1 small, measuring 3 millimeter in diameter and
2 0.85 millimeter in thickness. The tablet is housed
3 in a single-dose applicator as shown in the
4 picture.

5 The applicant's proposed indication is for
6 the management of moderate to severe acute pain,
7 severe enough to require an opioid agonist and for
8 which alternative treatment are inadequate in adult
9 patients in a medically supervised setting. The
10 30-microgram tablet is administered sublingually as
11 needed with a minimum interval of 1 hour between
12 the doses. The maximum dose is 12 tablets in 24
13 hours. It is given by a healthcare provider in a
14 certified medically supervised setting.

15 There are four issues to be considered for
16 today's discussion: the efficacy of sufentanil
17 30-microgram tablet for the management of acute
18 pain and the safety profile of the sufentanil
19 30-microgram tablet. In addition., a key
20 consideration is the risk of misplaced tablets and
21 the potential for accidental exposure. Finally, we
22 will consider the overall benefit-risk

1 considerations for the drug product. Details
2 regarding these issues will be reviewed during the
3 following FDA presentations.

4 Here are the key regulatory interactions
5 between the applicant and FDA. On October 4, 2011,
6 the applicant submitted an investigational new drug
7 or IND. On December 12, 2016, the new drug
8 application was submitted. On October 11, 2017,
9 FDA issued a complete response for the NDA.

10 A complete response means the agency did not
11 approve sufentanil sublingual 30-microgram tablet
12 for the management of acute pain. The complete
13 response letter outlined two deficiencies that
14 include, number one, there was an inadequate number
15 of patients dosed at the maximum dosing proposed
16 for labeling; and number two, the risk of misplaced
17 tablets. FDA and the applicant held a post-action
18 meeting on January 26, 2018 to discuss the
19 deficiencies and the applicant's proposal to
20 address them. The NDA was submitted on May 3rd.

21 For background, I will provide information
22 about the sufentanil sublingual 15-microgram tablet

1 program, which was a different application and
2 selected data from the sufentanil 15-microgram
3 studies used to support the safety of sufentanil
4 30-microgram tablet.

5 Sufentanil 15-microgram tablet has proposed
6 trade name of Zalviso. It was a different
7 sufentanil device combination which was designed to
8 be administered by a patient. The NDA received a
9 complete response primarily due to device related
10 issues. It was determined that it was reasonable
11 to use data from the sufentanil 15-microgram tablet
12 program to support the safety of sufentanil
13 30-microgram tablet based on the established
14 bioequivalence between two 15 microgram tablets
15 administered within 20 to 25 minutes and a single
16 sufentanil 30-microgram tablet.

17 Here's the overview of data supporting the
18 current NDA. The drug was developed on the
19 505(b)(2) regulatory pathway referencing Sufenta,
20 an injectable sufentanil formulation. The
21 application is also supported by its own sufentanil
22 30-microgram tablet development program and

1 selected safety data from the 15-microgram tablet
2 program.

3 Here is an overview of the sufentanil
4 30-microgram clinical development program. There
5 are a total of 5 clinical studies in the clinical
6 development program. Importantly, FDA only
7 included 4 studies in our analysis: a phase 1
8 pharmacokinetic study, SAP 101; a pivotal phase 3
9 placebo-controlled study, SAP 301; 2 open-label
10 studies, SAP 302 and 303.

11 FDA did not use data from study SAP 202 to
12 support the efficacy and the safety of sufentanil.
13 SAP 202 was a phase 2 placebo-controlled study.
14 The study used a different formulation, and the in
15 vitro data were not sufficient to bridge it to the
16 final to-be-marketed formulation.

17 I will now review the efficacy of sufentanil
18 30-microgram tablet. This table provides an
19 overview of the study SAP 301, which is the only
20 pivotal placebo-controlled study to evaluate the
21 efficacy of sufentanil 30-microgram tablet.
22 Briefly, the study was a randomized, double-blind

1 study of sufentanil 30-microgram tablet and placebo
2 administered as needed with a minimum of 16 minutes
3 between doses.

4 The study duration was up to 48 hours in
5 post-surgical patients following abdominoplasty,
6 open inguinal hernioplasty, or laparoscopic
7 abdominal surgery. All patients were required to
8 have at least 4 or higher on numeric pain scale at
9 the screening. Intravenous morphine was used as
10 rescue analgesia. Efficacy was measured using an
11 11-point numeric pain rating scale or NPRS.

12 The primary efficacy endpoint was the time
13 weighted summed pain intensity difference from
14 baseline over 12 hours or SPID12. Selected
15 secondary efficacy endpoint included the total
16 number of study medication and rescue medication
17 dosed over 24 hours and time-to-onset of meaningful
18 pain relief.

19 This figure shows the new pain intensity
20 scores and the 95 percent confidence interval over
21 24 hours. Of note, the figure used in the FDA
22 briefing book showed standard error intervals.

1 There was a separation in the pain curves between
2 sufentanil and placebo. In addition, there was a
3 statistically significant difference between
4 treatment groups for the primary endpoint, SPID12.

5 In addition to the primary endpoint, FDA
6 evaluated the secondary endpoint to see if it was
7 also supportive of the efficacy of sufentanil.
8 This table shows the mean and medium number of
9 rescue medication doses used during the first
10 12 hours. As you can see, there was very little
11 use of rescue medications in either treatment
12 group, but on average, subjects who received
13 sufentanil used fewer doses than subjects who
14 received the placebo. That was 0.4 versus 1.6.

15 Approximately 22 percent of patients
16 required rescue medication in the sufentanil group
17 compared to 65 percent in the placebo group in the
18 first 12 hours.

19 Another secondary endpoint was the median
20 time to meaningful pain relief, which was shorter
21 in the sufentanil group than in the placebo group.
22 That was 54 minutes versus 84 minutes. Time to

1 perceptible and meaningful pain relief was assessed
2 using the double stopwatch method. You'll note
3 that the applicant has emphasized different times
4 to onset, but FDA considers time to meaningful pain
5 relief as the most clinically relevant.

6 In summary, the primary and secondary
7 endpoints for study SAP 301 support the efficacy of
8 sufentanil 30-microgram tablets for the management
9 of acute pain. The applicant conducted 1
10 placebo-controlled trial, which was reasonable in
11 the context of this 505(b)(2) application to
12 confirm the effectiveness of the drug product in
13 the specific drug formulation and the sublingual
14 route of administration. However, the efficacy was
15 not compared with other available therapies.

16 Now I will review the safety of sufentanil
17 30-microgram tablet. Since the drug product is the
18 tablet-device combination, there are two main areas
19 that are important to consider in evaluating the
20 overall safety of this drug product. One was the
21 safety of sufentanil with the product-specific
22 sublingual formulation. The other is the safe use

1 of the device, which is associated with the risk of
2 misplaced tablet.

3 The safety database to support the
4 sufentanil exposure included data from 3 sufentanil
5 30-microgram studies and the selected data from 6
6 sufentanil 15-microgram studies. The data used to
7 evaluate the device and the risk for misplaced
8 tablet was from the human factors validation
9 studies and the risk assessment following
10 accidental exposure to sufentanil 30-microgram
11 tablet.

12 Regarding the safety database of sufentanil
13 exposure, there were a total of 646 patients
14 exposed. 323 of those patients were exposed to the
15 30-microgram tablet and 323 patients were exposed
16 to the 15-microgram tablet. In sufentanil
17 30-microgram program, 86 percent of patients used
18 less than 6 doses in the first 12 hours, and the
19 remaining, 14 percent used between 6 to 12 doses.
20 While the size of safety database was adequate for
21 the 505(b)(2) application, the number of patients
22 exposed to multiple doses were not adequate.

1 Regarding the safety evaluation of the
2 device and associated misplaced tablet, there are
3 3 events of dropped tablets in sufentanil
4 30-microgram phase 3 studies. In addition, errors
5 occurred in the first human factors validation
6 study. Dr. Townsend will review the details of the
7 human factors validation studies.

8 While data from both sufentanil 30-microgram
9 and sufentanil 15-microgram programs were analyzed
10 to support the safety of sufentanil, I will provide
11 a summary of the safety data from SAP 301. Because
12 this study was placebo controlled, it is important
13 to note that patients could receive rescue
14 intravenous morphine. Thus, this safety profile of
15 the placebo group includes rescue morphine
16 administration.

17 There were no deaths reported in SAP 301
18 during the study period. Two serious adverse
19 events or SAEs occurred in the placebo group. The
20 discontinuation due to adverse events were higher
21 in the placebo group compared to the sufentanil
22 30-microgram group. The common adverse events in

1 sufentanil 30-microgram treatment group were
2 consistent with the known opioid safety profile.

3 There were more patients who had oxygen
4 saturation less than 93 percent in the sufentanil
5 30-microgram group than in the placebo group. Two
6 patients in the sufentanil 30-microgram group had
7 oxygen saturation less than 92 percent. As we
8 know, respiratory depression is a known risk of
9 opioids and is included in the box warning in
10 opioid labeling.

11 Based on the overall safety evaluation in
12 our original NDA review, as already mentioned
13 briefly, FDA issued a complete response letter for
14 the original NDA with two deficiencies online.
15 First, there was an inadequate number of patients
16 dosed at maximum amount described in the proposed
17 labeling to assess the safety of sufentanil
18 30-microgram tablet.

19 Evaluation of safety at the maximum dosing
20 is important because sufentanil exposure
21 accumulates at multiple doses, as there is a nearly
22 fourfold increase in exposure and more than twofold

1 increase in the maximum concentration when dosed at
2 a steady state.

3 To address this deficiency, the applicant
4 was asked to collect additional data in at least 50
5 patients with postoperative pain sufficient to
6 evaluate the safety following the maximum dosing
7 proposed. Rather than collecting additional data,
8 the applicant proposed to decrease the maximum
9 daily dose from 24 to 12 tablets. In addition, the
10 applicant submitted a pooled safety analysis to
11 support the safety of proposed maximum daily dose.

12 The second deficiency with the possibility
13 of misplaced tablet poses a potential risk for
14 accidental exposure and improper dosing. To
15 address this deficiency, FDA told the applicant to
16 develop mitigation strategies to address the risk
17 and conduct another human factors validation study,
18 which the applicant completed after incorporating
19 FDA's recommendations. In addition, the applicant
20 submitted a risk assessment following accidental
21 exposure to sufentanil 30-microgram tablet.

22 The applicant performed pooled safety

1 analysis to support the proposed maximum 12 doses
2 in 24 hours. The pooled data was from one
3 sufentanil 30-microgram study and the selected data
4 from 3 sufentanil 15-microgram studies. The
5 analysis was based on total sufentanil dose
6 received dichotomized to less than 300 micrograms
7 or more than or equal to 300 micrograms.

8 There is significant limitations to this
9 safety analysis due to the differences in
10 sufentanil 15- and 30-microgram clinical programs
11 and due to the variety of factors that influence
12 the total dose received. However, despite these
13 limitations, the analysis was felt to be reasonable
14 in the context of supporting the maximum daily dose
15 proposed, as there was no clear relationship
16 between higher sufentanil dose and adverse event.

17 This slide highlights the safety concerns
18 associated with dropped tablet and applicant's
19 response to address it. sufentanil 30-microgram
20 tablet has a very small tablet size. There is a
21 significant safety concern of the possibility of
22 dropped tablet that leads to potential accidental

1 exposure, overdose, or even death, particularly in
2 the vulnerable pediatric population.

3 To address these deficiencies, the applicant
4 submitted a risk assessment following accidental
5 exposure to sufentanil 30-microgram tablet,
6 conducted the human factors validation studies, and
7 proposed risk evaluation and mitigation strategies
8 or REMS.

9 I will review the risk assessment following
10 accidental exposure to sufentanil sublingual
11 30-microgram tablet. The subsequent FDA
12 presentations will cover the next two topics.

13 To assess the risk following accidental
14 exposure to a 30-microgram tablet, the applicant
15 first used a population pharmacokinetic modeling
16 and simulation analysis to predict the sufentanil
17 plasma concentration following accidental exposure.
18 FDA agrees with applicant's methodology to assess
19 the predicted plasma concentration associated with
20 accidental dosing of sufentanil sublingual
21 30-microgram tablet in a 12-kilogram child.

22 Second, the applicant predicted the clinical

1 dynamic effects of accidental exposure to the
2 30-microgram tablet using the data and cited
3 literature from intranasal sufentanil in children
4 in pre-anesthesia settings. There are significant
5 limitations of these assessments because the data
6 were from different clinical scenarios.

7 While no definitive conclusions are possible
8 based on the data used for risk analysis. The data
9 in the literature did show the potential for
10 adverse events associated with an administration of
11 sufentanil, and the risk of respiratory depression
12 and death associated with accidental exposure
13 cannot be excluded.

14 In summary of the efficacy and the safety,
15 the sufentanil sublingual 30-microgram tablet was
16 effective in reducing pain intensity in one
17 placebo-controlled trial. The safety profile of
18 sufentanil sublingual 30-microgram tablet was
19 consistent with the typical opioid agonist.
20 However, given the small size of the tablet, there
21 is a concern for risks associated with misplaced
22 tablets such as accidental exposure and respiratory

1 depression.

2 Next, I will introduce Dr. Townsend to
3 provide the human factor evaluation.

4 **FDA Presentation - Otto Townsend**

5 DR. TOWNSEND: Good morning. Jim had every
6 intention to be here this morning, but mother
7 nature had other plans, so I'll be filling in for
8 him. My name is Otto Townsend, and I'm a team
9 leader with the Division of Medication Error
10 Prevention and Analysis, and I will present the
11 methods, evaluation of the human factors testing
12 for the sufentanil single-dose applicator.

13 In order to accomplish this, I will first
14 provide an overview of human factors engineering
15 and its role in the development of medical
16 products. Secondly, I will describe some of the
17 product characteristics for the sufentanil
18 single-dose applicator. And lastly, I'll summarize
19 the results from the human factors testing
20 conducted for the combination product.

21 What is human factors engineering? It's a
22 scientific discipline dedicated to understanding

1 the interactions between humans and a system in
2 order to optimize human well-being and overall
3 system performance. Moreover, it is a systematic
4 process to ensure that the design of the product is
5 optimized for safe and effective use.

6 In human factors engineering, we need to
7 consider how interaction between users, the
8 environmental conditions where the product will be
9 used, and a product-user interface will affect
10 overall product use. The term "product-user
11 interface" includes all points of interaction
12 between the user and the combination product,
13 including all elements with which the user
14 interacts, such as what the user sees, hears, or
15 touches. This can include packaging and labeling,
16 training when applicable, and all physical controls
17 and display elements.

18 The overall effect on product used by the
19 user, use environment, and product-user interface
20 leads to two potential outcomes: correct use or
21 use error. Eliminating or reducing design-related
22 hazards that contribute to unsafe or ineffective

1 use is part of the overall human factors
2 engineering process. The end goal is to ensure
3 that the product-user interface has been optimized
4 to improve overall safe and effective use of the
5 product. Human factors engineering aids in
6 improving the risk arising from design of a product
7 through a systematic approach.

8 Earlier, we spoke of the human factors
9 engineering process, and the combination of this
10 process is to validate through testing for safe and
11 effective use of the product. To accomplish this,
12 a human factors validation study should have a
13 clear objective to demonstrate that the combination
14 product can be used safely and effectively by the
15 intended users, for its intended uses, and
16 intended-use environments.

17 The testing should be designed such that the
18 test participants represent the intended users of
19 the product. All critical tasks are performed
20 during the test where a critical task is a task
21 that if performed incorrectly or not performed at
22 all could cause harm. The testing should also be

1 designed such that the product-user interface
2 represents the final design, and the test simulates
3 real-world use conditions.

4 Additionally, the data should be collected
5 and analyzed to determine whether the objective was
6 met. Even if the objective was met within the
7 study, it is still important to note that this does
8 not necessarily mean that after product goes to
9 market, that no use errors -- for example, dropped
10 or misplaced tablets -- will occur.

11 Now, I will describe some of the product
12 characteristics for the sufentanil single-dose
13 applicator. Use of the single-dose applicator is
14 detailed in the directions for use, and it's
15 performed by a healthcare provider.

16 The healthcare provider is instructed to
17 remove the white lock, place the single-dose
18 applicator tip under the patient's tongue. Depress
19 the green pusher to administer 30 micrograms
20 sublingual tablet from the tip of the single-dose
21 applicator to the patient's of sublingual space.
22 You can see the blue tablet at the bottom of the

1 picture. As mentioned in the previous
2 presentation, the tablet is 3 millimeters in
3 diameter and 0.85 millimeters thick.

4 Now, I will provide a high-level summary of
5 the human factors related regulatory history to
6 provide context on the interactions between AcclRx
7 and the agency. Several interactions occur between
8 AcclRx and the agency, and there were two
9 validation studies, one submitted in December 2016
10 and the other submitted in May 2018. AcclRx
11 conducted a second validation study because the
12 first did not demonstrate that the product-user
13 interface supported the safe and effective use of
14 the combination product by intended users for its
15 intended uses and intended-use environments.

16 Now, the details of the first validation
17 study submitted in 2016, the stated objective of
18 the study was to test participants' ability to
19 safely and accurately administer a sufentanil
20 sublingual tablet using the single-dose applicator.
21 There were a total of 45 healthcare providers that
22 took part in the study with 3 distinct user groups,

1 with 15 participants in each group, and live
2 patients were used. The study environment was a
3 simulated emergency room/

4 In the first validation study, healthcare
5 providers administered the product 4 times each,
6 and they had access to the directions for use and
7 were instructed to read the directions before
8 proceeding. After the administration, participants
9 were asked a series of 8 novice questions. Novice
10 questions are used to ascertain a participant's
11 understanding of a critical task that cannot be
12 directly seen by a study moderator. Lastly, the
13 moderator conducted a post-session interview with
14 each participant to elicit further feedback using
15 open-ended questions.

16 This slide displays the study results for
17 this first validation study. There were a total of
18 12 use errors amongst the three subtasks. Two
19 errors resulted in dropped tablets and 8 errors
20 were due to the participant not confirming the
21 tablet in the sublingual space.

22 We determined that the data did not support

1 the user interface and demonstrate that the user
2 interface supports safe and effective use. We
3 recommended changes to the directions for use steps
4 and graphics and recommended affixing a copy of the
5 full directions for use to the back of each foil
6 pouch that holds a single-dose applicator, and we
7 determined that a human factors validation study
8 was needed to evaluate the changes implemented in
9 the user interface.

10 Now, I will discuss the second validation
11 study. To do this, I will compare the differences
12 between the first and second validation studies,
13 and then provide information on the changes made to
14 the product-user interface prior to testing in the
15 second validation study.

16 First, the objective, participants used
17 tasks, knowledge task questions and post-session
18 interviews for the second evaluation study or
19 similar to the first study. We found these aspects
20 of the study acceptable. The differences between
21 the validation studies included training and the
22 study environment.

1 With training, participants in the first
2 validation study were requested to read the
3 directions for use. In the second validation
4 study, participants had access to the directions
5 for use but were not requested by the moderator to
6 read the directions prior to conducting the task.

7 The approach of not requesting participants
8 to read the directions for use was a design change
9 from the first study and more accurately reflects a
10 real-world environment because not all healthcare
11 providers receive formal training prior to
12 administering the drug. With respect to the study
13 environment, we find this acceptable given the
14 intended-use environments for the product.

15 Now, we'll compare the changes made to the
16 product-user interface after the first validation
17 study. In this slide, the directions for use steps
18 on the left were from the first study. Step 6
19 includes 3 steps combined into one. Depress the
20 plunger, deliver the tablet, and confirm placement.
21 The revised steps on the right were tested in the
22 second validation study. The combined steps were

1 separated into individual steps, and the step to
2 confirm placement of the tablet was revised to
3 include visual confirmation of the tablet.

4 This slide depicts the revisions to the
5 directions-for-use graphic depicting the anatomy of
6 the mouth. The graphics on the left were tested in
7 the first validation study, and the updated
8 graphics on the right were tested in the second
9 validation study. The graphics on the right are
10 the revised graphics that were intended to depict
11 the anatomy of the mouth more accurately and were
12 tested in the second validation study.

13 Thirdly, the graphics and the directions for
14 use were not labeled to provide clarity to
15 participants. AcelRx made revisions and labeled
16 each graphic as figure 1, figure 2, and so on.
17 AcelRx also added reference to the figures and the
18 directions to provide clarity and direction for the
19 reader.

20 Lastly, the pouch label that contains a
21 single-dose applicator included a condensed quick
22 guide for administering the dose as seen on the

1 left. It did not include all steps found in the
2 directions for use. This quick guide was tested in
3 the first validation study.

4 AcelRx x made revisions to include the full
5 directions for use, and they affixed them to each
6 pouch label that contains a single-dose applicator
7 using a leaflet and testing this change in the
8 second validation study. Again, the participants
9 were not asked to read the directions but had
10 access to the full directions for use on the pouch,
11 which more accurately simulates real-world use.

12 After incorporating these revisions, AcelRx
13 conducted the second validation study, and the
14 results were as follows. All participants
15 successfully completed the task, and there were no
16 dropped tablets. Therefore, based on the data
17 submitted, we determined the sponsor has
18 demonstrated safe and effective use of the product
19 by the intended users, for its intended uses, and
20 intended-use environments.

21 Now, Dr. LaShaun Washington-Batts will talk
22 about the risk evaluation and mitigation

1 strategies, or REMS, for the product.

2 **FDA Presentation - LaShaun Washington-Batts**

3 DR. WASHINGTON-BATTS: Good morning. My
4 name is LaShaun Washington-Batts, and I'm a
5 reviewer with the Division of Risk Management. I
6 will discuss the proposed risk evaluation and
7 mitigation strategies for sufentanil sublingual
8 tablets. This morning, I will provide a brief
9 background on risk evaluation and mitigation
10 strategies, also known as REMS; the risk associated
11 with the use of sufentanil sublingual tablets; and
12 lastly, the risk management options proposed by the
13 applicant and the agency.

14 First, I will provide a brief overview of
15 the REMS. A REMS is a drug safety program that can
16 be required by the FDA for certain drugs. A REMS
17 is designed to mitigate the risk associated with
18 drug use and include strategies beyond labeling to
19 ensure the benefits outweigh the risk of the drug.
20 The FDA Amendments Act of 2007 gave the FDA
21 authorization to require applicants and application
22 holders to develop and comply with firms programs

1 if determined necessary. The FDA has the authority
2 to require a REMS pre- or post-approval.

3 A REMS can include a number of components
4 such as a medication guide, communication plan,
5 elements to assure safe use, an implementation
6 system, and must include a timetable for submission
7 of assessments. If determined as a necessary
8 component of a REMS, the elements to assure safe
9 use can include the following: certification
10 and/or specialized training of the healthcare
11 providers that prescribes a drug; certification of
12 pharmacies or other dispensers of the drug; limited
13 settings for dispensing or administration of the
14 drug; having each patient using the drug subject to
15 certain monitoring; the drug is dispensed and/or
16 administered only with evidence of safe-use
17 conditions -- for example, a pregnancy tests -- or
18 enrollment of treated patients in a registry.

19 Additionally, ETASUs must commensurate with
20 a specific series of risks listed in the label.
21 They cannot cause undue burden or in patient access
22 to the drug, considering in particular patients

1 with serious or life-threatening diseases or
2 conditions and patients who have difficulty
3 accessing healthcare.

4 Now, we'll discuss the risk associated with
5 the use of sufentanil sublingual tablets. As you
6 have heard previously from Dr. Hu, the sufentanil
7 sublingual tablet is so small that it requires an
8 applicator for administration. The small tablet
9 size presents a risk of dropping or misplacement
10 during administration, which can lead to accidental
11 exposure. Accidental exposure, particularly in
12 children, can lead to respiratory depression,
13 overdose, and death. Also, similar to other
14 opioids, this product carries the risk of misuse,
15 abuse, and addiction.

16 The applicant has proposed a REMS with ETASU
17 to mitigate the risk of this product. The goal of
18 the applicant's proposed REMS is to mitigate the
19 risk of respiratory depression resulting from
20 inappropriate administration by ensuring that the
21 product is dispensed only within certified
22 healthcare facilities or services and informing

1 healthcare providers about the safe use of the
2 product, including proper administration and
3 monitoring. The applicant's proposed labeling
4 states that the product must be administered by a
5 healthcare provider and must not be dispensed for
6 home use.

7 The applicant also proposes the following
8 elements to assure safe use; that all healthcare
9 facilities and services that dispense the product
10 are certified and that the product can only be
11 dispensed to patients in medically supervised
12 settings.

13 In the applicant's proposed REMS, the
14 authorized representative will be required to
15 oversee and ensure compliance with the program
16 requirements.

17 1) Reviewing the REMS materials and the
18 prescribing information. The applicant has
19 proposed a safety brochure and a Dear Healthcare
20 Provider Letter as REMS materials.

21 2) Acknowledging that the healthcare
22 facility or service qualifies as a medically

1 supervised setting by meeting the following
2 proposed criteria. The setting has a licensed
3 pharmacy or healthcare provider with DEA
4 registration for Schedule II drugs who will oversee
5 ordering and administration of the drug. And the
6 setting has access to equipment and personnel
7 trained to detect and manage hypoventilation,
8 including use of supplemental oxygen and opioid
9 antagonists such as naloxone.

10 3) Ensuring the all staff involved in
11 dispensing or administering of the product are
12 trained on the REMS requirements.

13 4) Putting processes and procedures in place
14 to ensure that the product is not dispensed for use
15 outside of the certified healthcare facility or
16 service.

17 Now, I will discuss the FDA's REMS proposal
18 and provide the differences between the applicant's
19 and the agency's proposal. The agency's main
20 concern is accidental exposure, particularly in the
21 home.

22 The FDA's proposed REMS goal is to mitigate

1 the risk of respiratory depression resulting from
2 accidental exposure by ensuring that sufentanil
3 sublingual tablets are dispensed only to patients
4 in certified medically supervised healthcare
5 settings.

6 As proposed by the FDA, each certified
7 setting must designate an authorized representative
8 to attest to the following requirements on behalf
9 of the facility. Each setting must be able to
10 manage an acute opioid overdose, including
11 respiratory depression; train all relevant staff
12 that the product must not be dispensed for use
13 outside of the certified healthcare setting;
14 establish processes and procedures to verify that
15 the product is not dispensed outpatient, and train
16 all relevant staff involved in administration to
17 refer to the directions for use prior to
18 administration.

19 In general, we agree with the applicant's
20 proposed REMS with ETASU, but the FDA proposed REMS
21 includes a few differences from the applicant's,
22 which are important for the safe use of the

1 product. The FDA's focus is on the risk of
2 respiratory depression resulting from accidental
3 exposure. The applicant's proposed risk is
4 respiratory depression due to inappropriate
5 administration.

6 Secondly, the FDA's proposed REMS would
7 limit the use to certified medically supervised
8 healthcare settings. The applicant's proposed its
9 uses in certified healthcare facilities and
10 services, which are not well defined. If
11 sufentanil is restricted to the medically
12 supervised healthcare settings in which it was
13 studied such as hospitals, emergency departments,
14 or surgery centers, it will reduce the risk of
15 accidental exposure and ensure that the product is
16 administered by a healthcare provider who is able
17 to safely administer the product and manage acute
18 opioid overdose, including respiratory depression.

19 Next, Dr. Hu will end with the overall
20 benefit-risk consideration. Thank you.

21 **FDA Presentation - Ning Hu**

22 DR. HU: I will end the presentation with

1 overall benefit and risk considerations, which may
2 be helpful for the committee's discussion for the
3 overall efficacy and safety of sufentanil
4 sublingual 30-microgram tablet. The benefit of
5 sufentanil 30-microgram tablet included superiority
6 to placebo for analgesia in the management of acute
7 pain. Specifically, the primary and secondary
8 endpoints supported the efficacy of sufentanil
9 sublingual 30 micrograms in one placebo-controlled
10 study. The sufentanil sublingual 30-microgram
11 tablet would provide another option for the
12 management of acute pain.

13 The risks of sufentanil is similar to the
14 known opioid class safety profile and include
15 serious adverse events related respiratory
16 depression, addiction, abuse, misuse, accidental
17 exposure, and gastrointestinal events. There are
18 additional product-specific risks that are
19 associated with the small tablet size of the
20 Schedule II opioid product that might amplify risks
21 related to accidental exposure, misuse, and abuse.

22 If sufentanil sublingual 30-microgram tablet

1 was to be approved, we anticipate that it would be
2 only available through a product REMS program with
3 elements to ensure safe use that focuses on the
4 risks of accidental exposure. In the framework of
5 the benefits, risks, and risk management
6 considerations, we appreciate the committee's
7 considerations of the issues today. This concludes
8 FDA's presentation. Thank you for your attention.

9 **Clarifying Questions**

10 DR. ZACHAROFF: Thank you. We will now
11 entertain clarifying questions to FDA. Are there
12 any clarifying questions for the FDA? Please
13 remember to state your name for the record before
14 you speak, and if you have the ability to, please
15 direct your questions to a specific presenter.

16 Mr. O'Brien?

17 MR. O'BRIEN: Yes. I have two or three
18 questions. First, for Mr. Schlick [sic] I guess it
19 is, on slide number 9, just a question. In terms
20 of the participants, how was that derived? How did
21 you arrive at that being the population to test?

22 Where is Mr. Schlick? Oh, there you are.

1 MR. O'BRIEN: I'm over here; Townsend.
2 Schlick is not here. Actually, they proposed
3 these, and we found them acceptable. But the
4 reason that we found them acceptable is because
5 they represent the users that would actually use
6 the product. And initially, it was supervised
7 medical environment. And at that time, we had not
8 determined that we most likely would move toward
9 something that was more restricted. So I think
10 that's probably why the paramedics were initially
11 included. But they --

12 (Crosstalk.)

13 MR. O'BRIEN: You anticipated my question.
14 Thank you.

15 Dr. Washington-Batts, if that's the correct
16 name, again, or whoever gave the presentation for
17 slide number 8. Do you have a sample of the
18 product?

19 DR. WASHINGTON-BATTS: Do I have a
20 sample --

21 MR. O'BRIEN: Does anybody have a sample of
22 the product? It's fundamental, this issue or

1 safety regarding the size of the -- and I can tell
2 by the numbers, but I'd like to see the product
3 just to get a sense of --

4 DR. HERTZ: We don't have samples. We've
5 seen some placebo samples, but you can imagine it's
6 shown there to scale with a ruler. I'm not sure
7 what else to say.

8 MR. O'BRIEN: Okay. So you don't have one.
9 If we're going to be asked to assess safety, and
10 part of the safety is the product itself and the
11 size of it because it's so small, I can appreciate
12 it on the thing, but it's a different -- handling
13 and holding it just gives me a different sense.

14 I'd like to go to slide 18, then, and I just
15 want to make sure I understand. So the
16 restriction, as was just indicated, was from the
17 FDA. You're proposing -- if I can understand it
18 correctly, based on this slide and what the FDA is
19 proposing, that would therefore exclude ambulances
20 and first responders.

21 DR. WASHINGTON-BATTS: Yes, sir.

22 MR. O'BRIEN: That would?

1 DR. WASHINGTON-BATTS: Yes.

2 MR. O'BRIEN: Okay. Thank you very much.

3 DR. ZACHAROFF: Dr. Higgins?

4 DR. HIGGINS: Jennifer Higgins. I have a
5 similar question. I have a niggling feeling about
6 there not being any clarity about the practitioners
7 that will actually be permitted to administer the
8 medication. And I'm wondering if the FDA will set
9 any kind of licensure or certification requirements
10 for administration.

11 DR. LaCIVITA: Hi. This is Cynthia
12 LaCivita. I'm with the Division of Risk
13 Management. The attestations for the authorized
14 prescriber would be under the hospital setting, so
15 it would be who would normally administer opioids
16 in a hospital setting. So that would be under the
17 purview of the hospital.

18 DR. ZACHAROFF: Dr. Zeltzer?

19 DR. ZELTZER: Thank you. In looking at the
20 FDA's presentation, I understand the process
21 that -- questions that were asked that were then
22 addressed and the time sequence. At this point, I

1 guess, I didn't see anything that FDA required that
2 hasn't been met, so I'm -- can that be clarified by
3 maybe Sharon?

4 DR. HERTZ: Sharon Hertz. The company has
5 submitted the kinds of information that we have
6 asked of them. Yes.

7 DR. ZACHAROFF: Dr. Terman?

8 DR. TERMAN: Yes. Thank you. Can I ask
9 Dr. Hu why it didn't look or present today the 202
10 study. It had something to do with a different
11 formulation of the tablet, as I understood it.
12 Could you go into more detail about that? Because
13 I'm interested in that, as a bunionectomy seems to
14 be a more severe pain.

15 DR. HU: The formulation they used 202 study
16 is not bridged by our CMC review; decided it is
17 not bridged, the final to-be-marketed formulation.
18 So we're not including the study 202 in efficacy or
19 safety analysis.

20 DR. TERMAN: I'm sure that means something
21 to someone, but not bridged, what does that mean?

22 DR. MAYNARD: This is Janet Maynard from

1 FDA. Also as mentioned by the applicant, there was
2 lower exposure associated with the tablet that was
3 used in the 202 study, so it gets very difficult to
4 make assumptions about how that efficacy and safety
5 from that different formulation would apply. So
6 generally, in that sort of situation, we would not
7 consider the efficacy and safety information in our
8 assessments.

9 DR. TERMAN: Okay. Well, then I'm stuck
10 with the one that you did look at. On slide 18 in
11 Dr. Hu's presentation, which compares the placebo
12 and the drug over the period of time -- I don't
13 think -- oh, that is 18.

14 DR. MAYNARD: Janet Maynard from FDA. Do
15 you mean the efficacy results on slide 14?

16 DR. TERMAN: It's certainly possible; pain
17 intensity scores over 24 hours.

18 DR. MAYNARD: Yes. So that's FDA slide 14
19 in Dr. Hu's first presentation.

20 DR. TERMAN: That's it. Sorry. Yes. Can
21 you tell me how the pain scores are imputed when
22 rescue drug is given? I think I read that you

1 carry out the pain score for a few hours.

2 DR. REN: Hi. I'm the statistical reviewer,
3 Yi Ren, so I can answer this question. For
4 patients who used a rescue medication, the
5 pre-rescue observation was carried forward for
6 1 hour in the study. So that's the last pain
7 intensity that was observed prior to the use of
8 rescue medication.

9 DR. TERMAN: Okay. So just one hour.

10 DR. REN: Yes.

11 DR. TERMAN: So that's not -- there's a lot
12 more rescue medication used in the placebo,
13 although only 2 milligrams on average. And I just
14 wondered how close that placebo line might be if
15 they weren't imputed for an hour out of higher pain
16 scores. But it's only an hour, so there certainly
17 should be differences.

18 It's a little bothersome to me. The
19 indication is for pain severe enough to require an
20 opiate. And if they're really using 2 milligrams
21 of morphine for 24 hours, I just wonder what a
22 little ibuprofen might do for that and whether

1 we're really studying something that supports the
2 indication.

3 That's all I have. Thanks.

4 DR. ZACHAROFF: Thank you. Dr. Litman?

5 DR. LITMAN: Thanks. 'd like to ask just
6 some clarifications about the human factors. As I
7 try and think through this, I want to make sure I
8 really understand all the things that the FDA is
9 worried about. So as I think about it, the nurse
10 actuates this applicator and tries to get it
11 underneath the tongue, and then occasionally it
12 will bounce off somewhere into their nose or
13 whatever.

14 I'm trying to think of the things that could
15 go wrong, so please correct me if I'm wrong. One
16 is that the practitioner could catch it first and
17 divert it. That's always possible. The second is
18 that it gets lost in the bed sheets or the floor,
19 and then it's what? What are we trying to prevent
20 here, the theoretical situation that it's picked up
21 by a child somewhere in the ICU or the emergency
22 room? I'm trying to make sure I don't miss

1 anything here.

2 DR. HERTZ: So we're first trying to keep
3 this out of the house where a lost tablet could be
4 disastrous.

5 DR. LITMAN: Sure.

6 DR. HERTZ: So it's 3 millimeters by 0.84.
7 You really can't -- the reason it has an applicator
8 is because it's really not amenable to --

9 DR. LITMAN: Picking it up, sure.

10 DR. HERTZ: -- pulling it out of
11 a -- although there was a mention of the
12 hydromorphone tablet being small, I looked it up.
13 It's 5.4 by 2 points -- I mean, it's got a lot more
14 thickness. You can actually pick an oral
15 hydromorphone tablet up. You can hold it in your
16 fingers, and you can put it in your mouth. This is
17 really not --

18 DR. LITMAN: So it's thinner than a Tic Tac,
19 essentially.

20 DR. HERTZ: Yes, it's quite thin. So that's
21 why an applicator is necessary. When we went
22 through the Zalviso application, there were

1 episodes of it being found in the bed sheets.
2 Occasionally, if the device wasn't used properly,
3 it was left there. People were not aware of it not
4 having gotten into their mouth. You know,
5 nitroglycerin gives you a little burn. You can
6 tell if it's there. That's not what the experience
7 seems to have been here.

8 So the first intent with the REMS was this
9 is probably not a medication we want in an
10 uncontrolled setting because of that. Then in the
11 controlled setting, we want to make sure that it
12 goes where it's meant to go and that we don't want
13 patients who don't know they didn't get a drug, are
14 asking for more, and then perhaps they're
15 questioned, why do you want more opioid? We have
16 all these issues going on now.

17 Also, we think that given it's a Schedule II
18 product, it needs to be amenable to having
19 Schedule II controls within the hospitals standard
20 operating procedures available. So you have to be
21 able to track the dose.

22 So the goal was how do we keep this small

1 dosage form safe from situations where there could
2 be harm like outside of a controlled setting, and
3 then how can we make sure it's delivered when it's
4 supposed to be, that it's received, and that it can
5 work the way it's supposed to work.

6 DR. LITMAN: I mean, feasibly, the
7 most -- it's inevitable it will be lost. There's
8 just no way to prevent that. But I'm just trying
9 to think through the situation.

10 So you're in the emergency room and it's
11 lost. And like in the operating room when we
12 sometimes lose something -- it happens -- everyone
13 stops, and there's a search. And it's not metal.
14 It's not x-rayable [ph]. Sometimes it's not going
15 to be found.

16 DR. MAYNARD: This is Janet Maynard from
17 FDA. That's exactly our concern, that it would get
18 lost, or you would think maybe it was lost, but
19 then it's sort of not findable. Right? That it's
20 so tiny that if you can't find it, does that mean
21 that a child ingested it accidentally, or does that
22 mean it wasn't actually lost and the patient had

1 it?

2 So we're saying there's a lot of complexity
3 because of the small tablet size, and we really
4 appreciate you guys talking today and thinking
5 about that issue because I think that's the central
6 discussion question; that because it is so small
7 and it has that risk of not being found or
8 accidentally going into someone that it shouldn't
9 go to, what is the ramification of that?

10 DR. LITMAN: I can't even think about what
11 it would be -- they must lose oral meds on the
12 floor, or pills, all the time. I mean, it's just
13 inevitable. It's human nature. And if you think
14 about the process by which it's an opioid, what
15 kind of happens? And honestly, I don't even know,
16 but this would be even harder to find. Right? All
17 right. Thanks.

18 DR. MEISEL: I think the difference between,
19 say, a Vicodin or something that gets dropped and
20 lost than this, is that you'll know it because you
21 dropped it out of your hand; whereas this, you may
22 not know that it didn't come out of the applicator

1 or the applicator -- that kind of thing. I think
2 that's maybe the difference between this and other
3 kinds of tablets.

4 DR. ZACHAROFF: Thank you. Ms. Phillips?

5 MS. SHAW PHILLIPS: I appreciate some of the
6 differences in the detail in the FDA's proposed
7 REMS, particularly all relevant personnel. And
8 again, the concerns might be the ED physician that
9 hands one to a patient to take home if they have
10 recurrence of their migraine or some of those other
11 things, and really the challenge is for the
12 healthcare facility to make sure all those relevant
13 folks really are trained.

14 The question I have -- and I'm used to other
15 REMS that have limited sampling approaches to
16 validating that the REMS are monitored. And the
17 applicant's talking about looking at all facilities
18 in the first run and then some kind of sampling
19 approach.

20 So what would the FDA expect for ongoing
21 monitoring to make sure that the facilities are
22 really doing their due diligence? Because I think

1 doing education is an easy thing to check the box.
2 It's a hard thing to actually do, and document, and
3 maintain. But it's even harder to ensure that
4 there's auditing and monitoring going on in the
5 facilities to have the kind of controls that you'd
6 want over this product. I can't see it coming into
7 our hospital without a lot of internal auditing
8 that it was being used in appropriate patient
9 populations and who was actually getting it.

10 DR. ZACHAROFF: Thank you.

11 Mr. Thompson [sic]?

12 DR. LaCIVITA: Did you want me to answer
13 that?

14 DR. ZACHAROFF: Oh, I'm sorry. I didn't
15 realize it was a question.

16 DR. LaCIVITA: This is Cynthia LaCivita from
17 the Division of Risk Management. The training
18 would lie on the responsibility of the authorized
19 representative, and we understand -- I know that
20 the sponsor said that they're going to ensure that
21 every nurse is trained. That responsibility is
22 going to be the hospital's responsibility to do.

1 The sponsor can audit to see how that's done. We
2 haven't talked to them about their auditing plans
3 or their noncompliance actions yet.

4 So I think all that would need to be kind of
5 addressed from that perspective. But what one
6 hospital does to implement training may not be the
7 same that another hospital does. So it may be
8 different, and some hospitals may do it better than
9 others.

10 DR. ZACHAROFF: Mr. Thompson [sic], in your
11 slide 17, you showed us the photographs of what's
12 in the package, and I see an oxygen absorber packet
13 there. What's the purpose of the oxygen absorber
14 packet?

15 DR. TOWNSEND: It's a desiccant is the way
16 I understand it. And I think we actually asked
17 them to label it so that people would understand
18 what it was used for.

19 DR. ZACHAROFF: Okay. So that might imply
20 that if there was moisture in the package or if it
21 was exposed, it clearly says oxygen, that it might
22 in some way degrade the medication?

1 DR. TOWNSEND: That would be a chemistry
2 question that I probably am not the best person to
3 answer.

4 DR. ZACHAROFF: Okay. It just makes me
5 think about the fact that if there was some damage
6 to the packet that wasn't recognized, could that
7 potentially affect the medication in a negative
8 way?

9 DR. MAYNARD: This is Janet Maynard from the
10 FDA. We would defer to the applicant if they have
11 additional information about that.

12 DR. ZACHAROFF: Not necessary. Thank you.
13 And then just one other point about the lost tablet
14 in line with what Dr. Litman was saying. I'm not
15 potentially worried that a child may wander in and
16 find the lost tablet. I'm worried about possible
17 diversion at the healthcare facility level. If
18 this is a medication that could potentially be
19 administered to someone on an hourly basis, and
20 somebody is scanning packets and saying one for
21 you, one for me, this could be a potentially very
22 abusable and very easy to abscond with medication.

1 So I don't only look at accidental exposure
2 as a child getting their hands on it. I look at it
3 as possible nefarious people within the healthcare
4 setting getting their hands on it as well, so thank
5 you.

6 Dr. Fischer?

7 DR. FISCHER: Continuing on the discussion
8 of the REMS and the human factors safety? I think
9 that last point you made is, is important
10 especially because it sounds like patients aren't
11 necessarily aware if it's been placed sublingually.
12 As was pointed out before, it doesn't have the
13 tingle like nitroglycerin has. So if every other
14 dose were being diverted or something untoward like
15 that, that would be hard to pick up on.

16 I'm trying to still understand the piece
17 that was brought up about training. In the
18 applicant's presentation, the discussion sounded
19 like a strong emphasis on detailed training for all
20 relevant staff. And concerns were raised about how
21 realistic that is for the volume of nursing staff
22 that that might involve. In an institution,

1 similarly on page 18 of the REMS plan, it talks
2 about training staff.

3 If I understood the human factor, the
4 analysis that was acceptable in the end, that was
5 actually pretty minimal training. It was sort of
6 please look at the directions, but we're not going
7 to make you, and that still worked out ok. So is
8 that meant to be sort of a realistic not
9 everybody's going to do the training, but we end up
10 thinking it's still safe? I'm just trying to
11 reconcile all that as I look at these.

12 DR. TOWNSEND: Otto Townsend, FDA. Actually
13 in the first study, the participants were
14 instructed to read the directions. In the second
15 study, they were not asked to read the directions.
16 They were available for them to read if they chose
17 to, but they were not instructed to. To simulate
18 the real-world situation where someone has not been
19 trained properly, how would they interact with the
20 product.

21 DR. ZACHAROFF: Dr. Shoben?

22 DR. SHO BEN: I also have questions about the

1 human factors experiment. The first one is about
2 the sample size and how 45 was determined to be an
3 appropriate number, and having no failures out of
4 45 was considered to be proof that it was
5 appropriate.

6 DR. CHAN: Irene Chan with FDA. So human
7 factors studies, typically the validation studies
8 that we accept and utilize to support the user
9 interface, are qualitative studies, so they're not
10 powered to evaluate differences or changes in the
11 design; for example, superiority or lack of
12 superiority. It's a focused approach to try to
13 identify the greatest likelihood and the types of
14 use errors that may occur if a product were to go
15 to the market.

16 DR. MAYNARD: This is Janet Maynard from
17 FDA. Just to add one thing to that, when we're
18 evaluating these questions about use of a product
19 like this, we also think about what occurred in the
20 clinical studies. And it was mentioned by Dr. Hu
21 there were dropped tablets in that situation. So
22 we think about both human factors studies and

1 clinical experience.

2 DR. SHO BEN: I have one more question. The
3 other question is about the 3 patients, what were
4 those three scenarios and how different were they?
5 One of the dropped tablets in the clinical studies
6 was from a patient that was lying down. Was that
7 simulated and included in that study?

8 DR. TOWNSEND: I don't recall the details.
9 I have to look that up for you.

10 DR. ZACHAROFF: Dr. Terman?

11 DR. TERMAN: Sure. I just wanted to go back
12 to the lost tablet because it sounds to me -- at
13 first, I didn't think anything about that. I'm not
14 worried -- and we can discuss that later -- about
15 in-hospital diversion because that can happen with
16 any medication. The accidental diversion I wasn't
17 worried about because if you swallow it, it goes
18 away. But then I hear that there's adhesive on
19 there that a kid might not ask for a drink of water
20 if they were to put it in their mouth.

21 On the other hand, in the packet that was
22 presented, the sponsor did have a section on risk

1 assessment of dropped tablets that I didn't hear
2 really any acknowledgement of or even certainly not
3 a disputation of. So I would be interested in what
4 the take of the sponsor is since it appears to be
5 mostly theoretical PK work, but since several
6 people have brought it up, it might be worth
7 hearing what the sponsor has to say about the
8 dropped tablet issue.

9 DR. MAYNARD: Janet Maynard, FDA. If the
10 chair wants to hear from the sponsor, that's fine
11 with me --

12 DR. TERMAN: Sure.

13 DR. MAYNARD: -- or Dr. Hu covered that in
14 her presentation about FDA's assessment of the risk
15 assessment. But if you would like to hear from the
16 sponsor, and Dr. Zacharoff is in agreement, I think
17 that's reasonable.

18 DR. TERMAN: I'm sorry. Did Dr. Hu say that
19 FDA did not agree with that? I must have missed
20 that. I'm sorry.

21 DR. MAYNARD: On Dr. Hu's slide number 26,
22 she went over the risk assessment that I think

1 you're referring. Maybe we could bring up Dr. Hu's
2 first presentation, slide 26, please.

3 So it sounded like you were asking about the
4 assessment that the sponsor did to try and predict
5 what would be the potential clinical consequences
6 of a dropped hamlet. What the sponsor did was they
7 used data to first try and simulate what the plasma
8 concentration would be after accidental exposure,
9 and specifically we're focusing on children and
10 what the potential exposure would be in children.

11 They then went to the literature to see what
12 would be the anticipated clinical consequences of
13 those exposures, and there were a lot of
14 limitations to using the data and the literature to
15 support what would or wouldn't happen in the
16 setting of accidental exposure, because the
17 literature was from children who were
18 pre-anesthesia getting sufentanil, so those
19 children were highly monitored either pre or
20 intraoperatively.

21 So if there were any adverse events such as
22 apneic events, there was someone who is watching

1 them and could intervene quickly. And I think we
2 feel that's a different clinical scenario from a
3 child who might accidentally be exposed to this
4 product because I think that's one of the
5 fundamental issues, is you might not realize that
6 the child had accidentally been exposed to the
7 tablet. So using the literature that's available
8 about sufentanil is sort of limited in terms of
9 making clinical decisions about what the predicted
10 risk would be.

11 DR. TERMAN: I certainly agree that there
12 are limitations. I still wouldn't mind hearing
13 what the sponsor had to say, but that's entirely up
14 to you.

15 DR. ZACHAROFF: Dr. Palmer?

16 DR. PALMER: First, it's important that when
17 you think about what risk assessment is, it's a
18 question of the severity if the event were to occur
19 and then the probability of it actually occurring,
20 and combining that together to get a risk. And
21 that's what that third party did, was they looked
22 at both of those and combined them together, so

1 that the overall risk of a dropped tablet causing
2 harm was extremely low.

3 What I would first just show you
4 is -- sorry. I've got slide up. There we go.
5 That's just what I talked about there. So what I'd
6 first like to talk about is actually the severity
7 in blue. And again, you've got to first go through
8 all the steps of the probability of it actually
9 being dropped, not recognized by the nurse, not
10 recognized by the patient, having somebody who's a
11 vulnerable child in the room in a medically
12 supervised setting. If you go through the list of
13 8 things that all have to be multiplied together,
14 the probability is extremely low that you would
15 even get to a point of this vulnerable toddler
16 exposing themselves.

17 Next, what we did is, yes, while we were
18 evaluating toddlers that were about to undergo a
19 general anesthetic, we were actually using that
20 data to look at what would happen with their plasma
21 exposure. So we modeled based on everything we
22 could find in the literature of pediatrics who'd

1 been dosed intra-nasal sufentanil, and we looked
2 at, based on their clearance, based on their
3 weight, and we monitored what a single DSUVIA would
4 do for those patients. And what we found was, what
5 we considered the smallest ambulatory child would
6 be 12 kilos, that a single DSUVIA would reach a
7 peak plasma concentration of 200 picograms per mL.
8 And the reported literature suggests that as long
9 as the sufentanil concentrations are below 300
10 picograms per mL in the toddlers, that they're not
11 seeing the respiratory depression.

12 So we felt that, again, because the
13 severity is low and the probability is extremely
14 low, when those are combined together by this
15 third-party risk assessment, which we submitted to
16 the FDA, that the overall risk of a dropped tablet
17 causing harm in the medically supervised setting is
18 extremely low.

19 DR. ZACHAROFF: Thank you. Dr. Zeltzer?

20 DR. ZELTZER: So the two settings, the
21 emergency department and when a patient is out of
22 the PACU and on the floor where this drug may be

1 administered are probably in main places where
2 children might be, who are visiting the parent or
3 in the emergency department, family member with a
4 parent. From other studies in children, sublingual
5 transmucosal, even in attempts at providing
6 something sublingual, children tend to chew what is
7 in their mouth.

8 Do we know what the chewed bioavailability
9 is, especially per kilo or in a 12-kilo child?

10 DR. HERTZ: We know the oral relative
11 bioavailability is quite low. I think it was about
12 9 or 10 percent because of first-pass metabolism if
13 it's chewed and swallowed in an enteral route.

14 DR. ZELTZER: So chewing and dividing it in
15 particles, it's still that it's not a first pass,
16 so it doesn't matter whether it's swallowed whole
17 or chewed up.

18 DR. HERTZ: Yes. This formulation is
19 intended to deliver the sufentanil quickly, so
20 chewing it wouldn't necessarily accelerate that.
21 It's not extended release in any way.

22 DR. ZELTZER: Thank you.

1 DR. ZACHAROFF: Dr. Meisel?

2 DR. MEISEL: Steve Meisel with Fairview.
3 Just a quick follow-up from something Dr. Zacharoff
4 brought up about the desiccant packet that's in the
5 package. I'm reminded that suppositories have been
6 administered orally with a foil on it, and nurses
7 have administered those packages without taking out
8 the package of tablets.

9 Has FDA done any risk assessment of
10 swallowing the packets that couple this thing, that
11 it might be done; and if it is done, what the harm
12 might be, choking or otherwise?

13 DR. MAYNARD: Janet Maynard, FDA. No, we
14 have not done that.

15 DR. CHAN: Irene Chan, FDA. Also, that was
16 not a signal that came up in subjective feedback,
17 to our knowledge, within the human factors data.

18 DR. ZACHAROFF: Thank you. Mr. O'Brien?

19 MR. O'BRIEN: First of all, I greatly
20 appreciate the FDA's concern. Clearly, despite all
21 of the data, if you have a child, if it's my
22 grandchild that accidentally takes a pill in a

1 hospital, that's clearly a threat that I'm very,
2 very concerned about, for sure.

3 I was just wondering, I have to say that
4 anecdotally, I did have a case where I was
5 administered oral medication, a cocktail
6 medication, that included a 3 10 milligrams of
7 oxycodone, which one was later discovered in the
8 evening in my bed. It did not get into my mouth.
9 It did go down.

10 So it clearly does happen with other
11 medications. And I was curious with that, in that
12 did the FDA looked or did anybody look at any data
13 that says what is the incidence of that happening
14 with other opioids within the hospital environment?
15 Do we know that?

16 DR. HERTZ: No. And -- no.

17 MR. O'BRIEN: No.

18 (Laughter.)

19 MR. O'BRIEN: No and no. Okay. The other
20 question, which is sort of an aside, I was just
21 curious in terms of looking at these environments
22 as to where it's appropriate to have this. This

1 study, it was indicated by the sponsor and I think
2 it may have been in the FDA as well, that this
3 study was actually started with the Department of
4 Defense. I didn't see anything anywhere that said
5 where does the Department of Defense stand on this;
6 did they accept this as a good product for the
7 battlefield.

8 DR. HERTZ: We are not in direct
9 communication with DoD on this particular product.
10 I don't know what their assessment is.

11 MR. O'BRIEN: May I ask the sponsor if they
12 know what the assessment is?

13 DR. HERTZ: Sure. Dr. Zacharoff?

14 DR. ZACHAROFF: Sure.

15 MR. O'BRIEN: May I ask the sponsor, then?
16 Dr. Palmer?

17 DR. PALMER: Yes, the Department of Defense
18 came to us after they heard we were developing
19 Zalviso because, obviously, they can't use a fancy
20 electromechanical device out in the field. But
21 they were interested in replacing IM morphine.
22 Currently, they use 10 milligrams IM morphine, and

1 what happens during hypovolemic shock is that you
2 vasoconstrict to the muscles. So they would put 10
3 milligrams; wouldn't work, 10 milligrams. It's
4 just not getting to the brain.

5 So because of sublingual tissues, the
6 perfusion is maintained during shock because the
7 same perfusion that goes to the brain, they were
8 looking forward to using sublingual sufentanil
9 because they could maintain analgesia even in these
10 soldiers who are severely injured before they could
11 get an IV started in them. So they're excited,
12 from our communications with them, to have this
13 product.

14 MR. O'BRIEN: So they do accept DSUVIA as
15 you've developed.

16 DR. PALMER: Yes.

17 MR. O'BRIEN: Okay. Thank you.

18 DR. ZACHAROFF: Dr. Fischer? Oh, ok.

19 Dr. Kaye?

20 DR. KAYE: Thank you. Alan Kaye, LSU. I
21 just wanted to echo that we all have a lot of
22 amazing imaginations of scenarios. I'm pretty

1 confident that that there isn't an epidemic of
2 toddlers running around in these medical settings
3 that this drug will be used. Anything is possible,
4 but I think it's really -- some of this stuff we're
5 talking about is pretty extraordinary and unlikely.

6 Everyone has a story, so I'll just throw
7 mine in here. We had a syringe this big of 250 mgs
8 of fentanyl in the operating room that we lost with
9 a resident handing it to the attending to
10 administer, and we had 6 people looking for it for
11 2 hours, and we could not find it. It was later
12 found behind the back of the patient. How it got
13 there is still a mystery.

14 So there's always a one-in-a-million
15 setting, but I think the due diligence by the FDA
16 is outstanding in these presentations, but I have
17 no concern for what I've seen from company that is
18 presenting this medication today.

19 DR. ZACHAROFF: Okay. Just to make sure,
20 there are no further clarifying questions to the
21 FDA?

22 (No response.)

1 DR. ZACHAROFF: All right, then. We're
2 going to adjourn for lunch. We will now break for
3 lunch. We will reconvene in this room again at
4 1:00 p.m. sharp. Please take any personal
5 belongings you may want with you at this time.
6 Committee members, again, please remember that
7 there should be no discussion of the meeting during
8 lunch amongst yourselves. with the press, or any
9 other member of the audience. Thank you.

10 (Whereupon, at 11:52 a.m., a lunch recess
11 was taken.)

12
13
14
15
16
17
18
19
20
21
22

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. ZACHAROFF: Welcome back. We will now begin our open public hearing session. But before that, just an announcement.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

1 Likewise, FDA encourages you at the
2 beginning of your statement to advise the committee
3 if you do not have any such financial
4 relationships. If you choose not to address this
5 issue of financial relationships at the beginning
6 of your statement, it will not preclude you from
7 being able to speak.

8 The FDA and this committee place great
9 importance in the open public hearing process. The
10 insights and comments provided can help the agency
11 and this committee in their consideration of the
12 issues before them. That said, in many instances
13 and for many topics, there will be a variety of
14 opinions.

15 One of the goals today is for this open
16 public hearing to be conducted in a fair and open
17 way where every participant is listened to
18 carefully and treated with dignity, courtesy, and
19 respect. Therefore, please only speak when I
20 recognize you, and thank you for your cooperation.

21 Will speaker number 1 please step up to the
22 podium and introduce yourself? Please state your

1 name and any organization you are representing for
2 the record, please.

3 DR. EKOLA: Good afternoon. My name is Tim
4 Ekola. First of all, I'd like to thank the
5 advisory committee for allowing me to speak today.
6 I'm the director of pharmacy at Sparrow Hospital.
7 We're a 700-bed, level 1 trauma center located in
8 Lansing, Michigan. Also, I'd like to disclose that
9 AcelRx has paid for my transportation and lodging
10 for this meeting. That being said, I am speaking
11 only for myself.

12 I've been in the pharmacy profession for
13 over 30 years. I began my career as a hospital
14 corpsman in the Navy. I finished with 24 years of
15 service as a pharmacist and retired as a lieutenant
16 commander. During my time in the Navy, I was
17 embedded with the Marines as a hospital corpsman at
18 Camp Pendleton and spent the last part of my career
19 at Landstuhl Army Regional Medical Center from 2006
20 to 2013 in support of Operation Enduring Freedom
21 and Operation Iraqi Freedom for that time.

22 When I first learned about DSUVIA, I was

1 intrigued about the unique delivery system and its
2 niche in hospital, in the ER, and in the surgery
3 arena. As I learned more about the
4 pharmacokinetics and its comparison to other
5 similar opioid medications, I felt the product
6 provided a unique opportunity for healthcare
7 providers, as well as providing safe and
8 appropriate pain management. However, I'm here
9 today to speak about my military perspective and
10 its unique perspective regarding use in trauma and
11 in the battlefield.

12 As we heard stated earlier today, we've seen
13 many instances of service members who were
14 overdosed on morphine as medics tried to relieve
15 pain by giving additional IM morphine doses. Many
16 of those wounded are bleeding out, and they're in
17 hypovolemic shock. This trauma reduces the
18 availability of the morphine due to the
19 under-perfusion of the peripheral muscles, and this
20 lack of perfusion often means a second, third, or
21 even a fourth dose of morphine for that wounded
22 patient.

1 Once that patient is on their way to more
2 definitive care and is receiving IV solutions,
3 re-perfusion occurs. And when this happens, the
4 morphine is picked up from the muscles, and we see
5 the effects of that dose stacking of the morphine
6 crossing into the brain, and this can lead to
7 respiratory distress and even death.

8 Imagine yourself being a medic in the heat
9 of battle or in a noisy rescue helicopter, unable
10 to determine the signs and symptoms of overdose,
11 the noise of your surroundings overwhelming you,
12 and not being able to hear the alerts and the
13 sounds of different alarms such as pulse ox.

14 DSUVIA not only provides opportunities in
15 our own communities for our own family members and
16 friends, but it potentially saves lives on the
17 battlefield. And when considering the battlefield
18 analgesic properties, DSUVIA fits that picture.
19 The delivery device that we've seen provides a
20 robust stability in the face of that harsh field
21 environment. There's a straightforward method of
22 delivery, making it easier for that gloved medic to

1 deliver the medication. We see the rapid onset of
2 medication with a low risk of adverse events. And
3 as mentioned earlier, with the sixth item
4 assessment of impairment, there's less altered
5 mental status of that patient.

6 In addition, the sublingual delivery of
7 sufentanil offers potential for field-based pain
8 relief. We've seen the fat soluble 1500 times more
9 soluble than morphine. We see the sublingual
10 tissue perfusion maintained during shock; that was
11 mentioned earlier. The clinical data supports a
12 greater reduction in the pain intensity in the
13 first 4 hours as compared to IV or IM morphine.
14 And the elimination of needle-stick injuries and
15 the associated risk of infection is also important.

16 So as was stated earlier this morning,
17 DSUVIA reaches equilibrium between the blood and
18 the brain quickly, and pain relief is comparable to
19 the injectable opioid medications. DSUVIA has the
20 potential of reducing overdosing in the battlefield
21 and saving lives. I'd like to thank you for your
22 time and listening to my perspective this

1 afternoon.

2 DR. ZACHAROFF: Thank you. Will speaker
3 number 2 please step up to the podium and introduce
4 yourself? Please remember to state your name and
5 any organization you are representing for the
6 record.

7 DR. RITTER: Good afternoon. My name is
8 Mike Ritter. I'm the medical director of the
9 emergency department at Mission Hospital and
10 Children's Hospital at Mission that's in southern
11 California. AcelRx sponsored my travel and hotel
12 to attend the meeting today.

13 I'm here speaking as a practicing emergency
14 physician, and I look at this medication as
15 something that I can add to my toolbox to treat
16 patients with acute pain. We have a number of
17 patients that arrive in the ER by paramedics that
18 do not have an IV when they come in, not to mention
19 all the patients that walk in that have acute
20 injuries or we need to treat their pain.

21 We have a CMS metric that we have to follow,
22 OP-21, which is an outpatient performance metric.

1 That metric wants us to start pain medication or
2 analgesia within one hour of arrival for patients
3 with long bone fractures. What we found by meeting
4 these goals, and we're currently at about 40
5 minutes, is that patients in addition to getting
6 pain relief also have a better experience in
7 emergency departments. So our customer
8 satisfaction goes up, which means that we're
9 helping them through their suffering when they come
10 in with acute injuries.

11 Some of the issues that come up while we've
12 initiated this process to try and initiate
13 analgesic pain therapy early is that most of our
14 patients arrive as walk-ins. They don't have IV in
15 place. And if we want to start an oral pain
16 medication, there are issues that come up. One,
17 patients with acute pain many times have nausea
18 and/or vomiting, so they can't take an oral pain
19 medication. This would solve that with the
20 sublingual administration.

21 Secondly, when I'm assessing somebody that's
22 got a fractured long bone, I don't always know

1 until I have an x-ray if this is someone that's
2 going to need surgery or not, and I have to make a
3 guess about am I going to give them an oral pain
4 medication while I'm waiting for their x-ray with
5 the risk of them drinking water and the anesthesia
6 [sic] saying, well, they had a glass of water.
7 It's going to delay their surgery a couple of hours
8 because of that. This would address that as well.

9 Other issues, you say, well, why don't you
10 just give intramuscular pain injections? A lot of
11 our elderly patients are on blood thinners,
12 Coumadin and the novel oral anticoagulants. And
13 when you give an intramuscular injection, they get
14 a hematoma, and there are complications from that
15 as a result, so this would help to get around that.

16 I see this as a bridge for patients that do
17 have serious injuries until we can get an IV
18 started. There were some questions that were
19 raised by the committee about patients that can't
20 get an IV by paramedics, and I actually have some
21 statistics on that from our trauma database. We're
22 a busy trauma center. We see about 2600 traumas a

1 year. And of those, one-third are over the age of
2 65. And if you take that subset of patients, 52
3 percent, paramedics are not successful of getting
4 an IV in the field. So they arrive in the trauma
5 suite with no IV, and we've got to get an IV
6 started.

7 In the meantime, we grapple with what we're
8 going to give them for pain medication.
9 Additionally, with the elderly, the reason the
10 paramedics can't get an IV started is they're a
11 tough stick. Even our skilled nurses, it may take
12 them several tries to get a line started.

13 The last thing I'd like to address, and this
14 was another comment that I heard from the
15 committee, is I've worked at this hospital with
16 both pediatric and adult ER for 22 years. During
17 that timeframe, we've seen over one 1.5 million
18 patients, and I have never had a case at our ER
19 where a child has eaten a pill that's fallen on the
20 floor.

21 I know that's a theoretical concern. My
22 personal experience as a practicing emergency

1 physician is almost all kids that get into
2 medication, it's the grandparents' medicines in the
3 little plastic container that they leave in the
4 bedroom when they come over to visit or babysit the
5 kids.

6 Thank you for allowing me to speak today and
7 have a good day.

8 DR. ZACHAROFF: Thank you. Will speaker
9 number 3 please step up to the podium and introduce
10 yourself? Please state your name and organization
11 you are representing for the record.

12 DR. BENDER: Good afternoon. My name is
13 Frederick Bender, and I'm a licensed pharmacist in
14 South Carolina. For the past 40 years, I have
15 worked as a director of pharmacy
16 for large health systems, which have included acute
17 care hospitals, long-term care facilities, doctors'
18 offices, and retail pharmacies. I have been
19 involved in every aspect of inpatient and
20 outpatient care over the course of my career.

21 I continue to work today as a consultant
22 pharmacist and compliance officer for the

1 Greenville health system in Greenville, South
2 Carolina. I would like to offer my personal
3 comments today on the new product DSUVIA from an
4 acute care hospital perspective. And from a
5 disclosure, I would like to mention that my travel
6 expenses to attend the meeting today have been
7 supported by the sponsor.

8 I believe DSUVIA represents a new and unique
9 dosage form of a well-known medication. Sufentanil
10 is a safe and effective opioid analgesic with which
11 we are very familiar. One of the significant
12 advantages of DSUVIA is that it is rapid-acting and
13 administered in a noninvasive, sublingual form.
14 This can be very advantageous in our patients
15 requiring immediate treatment in hospital emergency
16 departments and other medically supervised
17 settings.

18 In addition, hospitals are accustomed to
19 ordering, stocking, and administering many
20 different types of controlled substances. The
21 entire medication acquisition and administration
22 process have been designed to provide a safe and

1 secure system while deterring diversion. We have
2 intricate automated systems in place designed to
3 manage controlled substances such as DSUVIA.

4 We manage these medications through
5 automated dispensing cabinets, which are in all of
6 our emergency departments and nursing units. These
7 cabinets electronically interface with our
8 electronic medical records to create systems that
9 are designed to improve medication, documentation,
10 and accountability while deterring drug diversion
11 and abuse. Thus, we would not need to implement
12 any new systems or controls to fully manage DSUVIA
13 storage and administration. These automated
14 systems mitigate the risk of medication abuse and
15 diversion even without a REMS requirement, which
16 has been recommended for DSUVIA.

17 I believe that DSUVIA is less susceptible to
18 diversion and abuse as we now see with other
19 narcotics since DSUVIA is a discreet, sublingual
20 dosage form that does not require special
21 measurement or preparation as do other injectable
22 narcotics such as morphine. This simplifies

1 administration and eliminates the need for wasting
2 of unused drug, which will save our staff time and
3 reduce the likelihood of diversion.

4 Other clear injectable narcotics such as
5 morphine must be wasted using a detailed process in
6 hospitals, which is prone to error and
7 manipulation. Unfortunately, drug abusers have
8 taken advantage of this wasting process to divert
9 drugs which should have been otherwise wasted; for
10 example, by substituting water in place of other
11 clear liquid injectables such as morphine or
12 hydromorphone. Such substitutions are very
13 difficult for healthcare systems to detect and
14 correct.

15 I would also like to make a couple of other
16 comments on a couple of points that were raised
17 earlier in this morning's presentations regarding
18 dropped doses. Our system has a large children's
19 hospital and a pediatric emergency room, and in all
20 of my years as a hospital pharmacy director and
21 reviewing hundreds and thousands of medication
22 errors, I cannot really remember ever seeing one

1 involving a child getting a medication off of the
2 floor or in any other areas of the hospital or the
3 ER. So in my experience, that really is a very low
4 likelihood.

5 Another point was made in regards to
6 opportunity for diversion with DSUVIA, and I think
7 my response to that would be that, really, every
8 controlled substance that we handle and deal with
9 today in our hospitals is really subject to
10 diversion. And we really work very hard to
11 maintain our systems of control and accountability,
12 and I think that we could do that very easily with
13 DSUVIA.

14 In conclusion, I believe that DSUVIA offers
15 a unique new, safe and effective option for our
16 hospitals to provide noninvasive analgesia for our
17 patients while deterring diversion and abuse.
18 Thank you for allowing me to provide these comments
19 today.

20 DR. ZACHAROFF: Thank you. Will speaker
21 number 4 please step up to the podium and introduce
22 yourself? And please remember to state your name

1 and any organization you are representing for the
2 purposes of the record.

3 DR. FOY: Good afternoon, everyone. My name
4 is Maria Foy, and I'm a clinical pharmacy
5 specialist in pain and palliative care at Abington
6 Jefferson Health, part of the Thomas Jefferson
7 University system outside of Philadelphia. At this
8 time, I would like to disclose that AcelRx has paid
9 for my transportation and lodging for this meeting.
10 All statements that I'll be making today are of my
11 own accord.

12 My scope of practice includes both chronic
13 and acute pain and both non-cancer and cancer pain.
14 I've been practicing pain management in my
15 institution over the last 10 years and recently
16 have been the recipient of a patient safety award
17 for my work with opioids in providing education,
18 developing guidelines, developing policies and
19 procedures, and also developing order sets for our
20 electronic medical records.

21 I am also an expert speaker for the
22 Institute for Safe Medication Practices, ISMP,

1 where I've done multiple webinars on opioid therapy
2 with a webinar recently being on acute pain
3 management entitled, Opioids in the Acute Care
4 Setting: Safety is within Our Reach. But I'm here
5 today to speak about a new product, a short-acting
6 opioid dispensed with a very novel delivery system.

7 In the institutional setting -- that's where
8 I work -- miscalculating dose equivalence between
9 different opioids and even between oral and IV
10 formulations of the same opioids are relatively
11 common. In addition, we see as we're talking about
12 morphine and different injectable medications and
13 clear liquids, they also come in different
14 concentrations. A concentration can be picked up
15 accidentally where it can cause an error and harm
16 to our patients. Since DSUVIA is only available in
17 a 30-microgram single dose, most of those errors
18 will not be possible, and we see this as a much
19 safer drug.

20 We also all know about whoever works in a
21 hospital system have been deluged with opioid
22 shortages, where we are constantly having to get

1 different medications, different concentrations,
2 depending on what's available at that time. The
3 Institute for Safe Medication Practices recommend
4 that you only keep one formulation and one
5 concentration of each drug, but that has been
6 impossible to comply with. So we run into errors
7 where we're using something we're not familiar with
8 or we're assuming it's something else. So DSUVIA
9 kind of mitigates those errors in our institution.

10 DSUVIA has a very quick onset of action.
11 Potency and dosing errors are minimized because of
12 its single dose. We also see safety in patients
13 that may have comorbid kidney disease and liver
14 disease, as this drug doesn't have any active
15 metabolites, so it's much safer for that patient
16 population to use.

17 Personally, I've been able to handle the
18 system, the demo with the placebo pill. What I've
19 been able to notice, it's clear, and you can see
20 the tablet in that delivery system itself. There's
21 a lock on it to prevent activation errors. Once
22 you activate it, you're not able to pull that back

1 and put another dosage form in there and divert
2 that drug. We all tried. That activator was
3 impossible to disassemble. We really tried for a
4 few good 5 minutes, and we were not able to
5 disassemble that activator.

6 So based on my clinical expertise, I feel
7 that DSUVIA would address an area for a safe,
8 quick, noninvasive opioid in a monitored setting.
9 I'd like to thank you today for your attention and
10 allowing me to speak.

11 DR. ZACHAROFF: Thank you. Will speaker
12 number 5 please step up to the podium and introduce
13 yourself? Please remember to state your name and
14 any organization you are representing for the
15 record.

16 DR. MINKOWITZ: Good afternoon, and thank
17 you all. My name is Harold Minkowitz. I'm an
18 anesthesiologist from Houston, Texas. I am also
19 the director of clinical investigation with
20 Research Concepts. At the outset, I'd like to
21 mention that AcelRx has supported my travel and
22 expenses to attend this meeting today, but I will

1 be describing to the committee my personal
2 experience as an investigator.

3 I've been involved in clinical research,
4 particularly acute pain research and the study of
5 novel drugs for the treatment of acute pain, for
6 the last 27 years. As an anesthesiologist, I'm
7 very aware of intravenous sufentanil. I've used it
8 intraoperatively in many cases, particularly
9 cardiac and surgical cases because sufentanil is a
10 cardiac-stable opioid with predictable effects.

11 When I heard about a sublingual form being
12 developed, I was really excited to research its
13 utility to treat patients' pain postoperatively. I
14 still remember very clearly the very first patient
15 dosed with sufentanil. Her pain was nicely
16 controlled, but she demonstrated an effect that I
17 hadn't seen before with an opioid. She was
18 comfortable, but she was also awake and lucid, and
19 she didn't seem to be sedated and groggy from the
20 opioid. I wondered was that just her unique
21 response or was sufentanil somehow different to
22 other opioids in OA [ph] patients, as I'd only

1 dosed patients under anesthesia with this drug.

2 Over the last decade or so, I've dosed over
3 200 patients in various clinical trials with
4 sublingual sufentanil, and I found its analgesic
5 profile to be remarkably consistent and provides
6 excellent analgesia with minimal sedation. Because
7 of what I've seen, I have a very high comfort level
8 with its safety.

9 I was involved with both the Zalviso and the
10 DSUVIA trials, Zalviso, as you recall, being the
11 patient-controlled system. With both products, the
12 patients were very happy with an analgesia
13 provided. And as an investigator, I would often
14 ask them how's it working for you. And they were
15 very happy with the drug.

16 I would ask them how long before they felt
17 an effect, and many patients would relate a squishy
18 sensation under their tongue after dispensing the
19 drug, and they would say their pain was relieved
20 pretty rapidly, they'd say within 15 minutes or so.
21 From my own observations, this is much faster than
22 the to-be-administered oral medications.

1 Now, we discussed this morning, discussed
2 about the dropped tablets discussed this morning,
3 and at my site, we did have one dropped tablet,
4 which was found and accounted for. I know that out
5 of 1800 patients in the DSUVIA trials, there were
6 3 dropped doses, all of which were found with 100
7 percent drug accountability.

8 As one of the few people in the U.S. with
9 this much experience with the drug, I sometimes
10 felt strange with the zeal that I exhibited for
11 sublingual sufentanil. People would ask me, why do
12 you like this drug so much? So I'd tell them the
13 onset of action is great. The analgesia is good.
14 People are clear-headed. Physical therapist loves
15 it because their patient could rehab so well.
16 Nurses and doctors all liked it. But I couldn't
17 really express my observation like that, and I had
18 to tell them, once you see the effects, you will
19 understand.

20 I recently attended a meeting in Europe, and
21 I found physicians there also had the same
22 enthusiasm that I did for the Zalviso system or

1 sublingual sufentanil. And they are prescribing
2 the drug in their hospitals as well to treat their
3 patients. One of the physicians speaking at the
4 meeting seemed to mirror my experience exactly, and
5 I couldn't believe it.

6 In his concluding remarks, when he told the
7 audience, once you see the patient use this
8 medication, you will understand the difference. At
9 that moment, I must say, I felt vindicated. I was
10 excited that European doctors who are using this
11 drug in their daily practice had the exact same
12 experience that I did as a clinical researcher.

13 In conclusion, based on my own direct
14 experience with my patients, DSUVIA is safe and
15 effective, and it provides for the first time the
16 ability for us to provide noninvasively and rapidly
17 the treatment of acute pain in opioid-naive
18 patients. Thank you for your time.

19 DR. ZACHAROFF: Thank you. Will speaker
20 number 6 please step up to the podium and introduce
21 yourself? Please remember to state your name and
22 any organization you are representing for the

1 purposes of the record.

2 DR. ALADDIN: Good afternoon. My name is
3 Meena Aladdin, and I'm here on behalf of Public
4 Citizen, a public advocacy group out of DC. We
5 have no financial conflicts of interest.

6 IV sufentanil was approved in 1984. It is 5
7 to 10 times more potent than its [indiscernible]
8 fentanyl, making SST or sufentanil sublingual
9 tablet the most potent opioid in this dosage form.
10 This drug has raised concerns on safety and
11 efficacy in its initial submission.

12 SST, this applicant has addressed
13 deficiencies outlined by the FDA, and they have
14 shown efficacy as compared with a placebo, but they
15 have failed to demonstrate sufficient evidence that
16 the efficacy of SST is superior to available drugs
17 on the market, and that other drugs on the market
18 cannot accomplish what it can accomplish. So this
19 product does not address any unmet medical need.

20 As stated in the FDA briefing packet, there
21 is a number of available opioids already on the
22 market that can be administered in a number of

1 ways, including sublingually. Since SST was only
2 compared to a placebo completed in one phase 3
3 study, there are no data available on the efficacy
4 of SST compared to other therapies.

5 Overall, as the committee has pointed out,
6 there are two main issues that were presented.
7 There is the issue of demonstrating safety of SST
8 in patients requiring maximum dosing proposed for
9 labeling, and finally the risk of misplaced
10 tablets. Now, the applicant has demonstrated that
11 they have addressed these concerns, and upon
12 initial review, there was a safety with the maximum
13 dose that was proposed, and that was also an
14 inadequacy in the data of repeated doses as well as
15 adverse effects occurring at non-steady state
16 levels. And they've addressed this by reducing the
17 maximum dose, but also they pooled the safety
18 studies from previous SS studies and created pool
19 8.

20 But it is important to recognize that there
21 are limitations to what they have done to the
22 safety studies. Administration of SST was given as

1 needed, which complicates the dose and plasma
2 concentration understanding. Furthermore, also
3 analyses was based on the dose and concentration
4 within the first 24 hours, not accounting for times
5 after that.

6 In terms of misplaced tablets, the size
7 remains to be an ensuing concern. It's also very
8 potent. The applicant has addressed improper
9 device use by modifying the directions for use and
10 also carrying out human factors validation studies
11 for dropped tablet valuations.

12 Finally, inappropriate tablets and
13 sublingual placement, which was also addressed by
14 the modification of a DFU and restriction to
15 healthcare settings that fall into specific
16 category, that it remains unclear how this
17 restriction is going to translate to the
18 non-clinical real world.

19 In conclusion, we are urging the advisory
20 committee not to approve this drug for the
21 following reasons. First, SST does not provide any
22 additional unique advantages not achievable with

1 currently available alternative opioids. That has
2 not been demonstrated. Secondly, its high potency
3 in the context of new oral dosage form may present
4 unique, serious adverse effects that have not been
5 accounted for in addition to the respiratory
6 depression that we know it causes.

7 Finally, inconsistent with a precautionary
8 principle, the lack of any unique benefit and an
9 unmitigated concern for unique risks mandate
10 non-approval. I thank you for your time and for
11 listening to me.

12 DR. ZACHAROFF: Thank you. I'm not sure if
13 you're here. Speaker number 7, are you here?

14 (No response.)

15 DR. ZACHAROFF: Okay. We'll check back
16 before we close.

17 Speaker number 8, would you please step up
18 to the podium and introduce yourself? Please
19 remember to state your name and any organization
20 you are representing for the purposes of the
21 record.

22 DR. HUTCHINS: Good afternoon. My name is

1 Jacob Hutchins. I'm an associate professor at the
2 University of Minnesota in the Department of
3 Anesthesiology. I'm also the director of the
4 regional anesthesia acute pain and ambulatory
5 anesthesia division and executive medical director
6 of the ambulatory surgery center at the University
7 of Minnesota. In full disclosure, I was an
8 investigator in the phase 3 trials of DSUVIA, and
9 my travel and lodging was covered by AcelRx.

10 I'm here today to discuss acute pain control
11 and the role that DSUVIA can play in treating our
12 patients that are in institutions across the United
13 States. Acute pain control remains one of the most
14 important, if not the top concern, of patients
15 coming into surgery today, and multiple surveys
16 from the 1990s, 2000s, and 2000 teens have shown
17 that a good portion, the majority of patients,
18 still have moderate to severe pain after surgery.

19 Poor pain control can lead to many negative
20 effects on patients, not limited to impacts on
21 immune function, hypercoagulability, and decreased
22 GI motility. Furthermore, uncontrolled acute pain

1 can lead to persistent pains issues after surgery
2 and even impacts the overall healthcare systems as
3 it can contribute to delays in PACU stays, delays
4 in discharged from the hospital, and readmissions
5 for pain.

6 The optimal approach to acute pain
7 management as a multimodal approach involves two or
8 more different types of pain medications to treat
9 this. For those surgeries or injuries in which
10 acute pain is mild or mild to moderate, this can
11 usually be treated with non-opioid medications such
12 as acetaminophen, nonsteroidal anti-inflammatory
13 drugs, or local anesthetics.

14 However, when patients experience moderate
15 or moderate to severe pain, opioids are typically
16 needed in conjunction with the aforementioned
17 medications. This has been shown with both the
18 American Society of Regional Anesthesia and the
19 American Society of Anesthesiologists, both of
20 which I'm a member of, that I've recommended in
21 these moderate and moderate to severe patients that
22 opioids we need to treat these patients.

1 I do believe this is an unmet need, and we
2 see this with the advent and the more progression
3 of enhanced recovery after surgery programs and
4 institutions across United States. There's a push
5 for the move away from intravenous opioids in these
6 patients that are having moderate to severe pain to
7 improve their recovery and get them moving and
8 participated in therapies and out of the hospital
9 sooner.

10 What happens now is we move from an IV to an
11 oral opioid, with the oral opioids having a slower
12 onset of action. And because they're in this
13 moderate to severe pain, we've seen an escalation
14 in the dose of the oral opioids. So we've
15 oxycodone or Vicodin dosages from the 5 to 10
16 typically being moved up to 15 to 20. And
17 unfortunately, as providers are less comfortable
18 with these medications, as they get through their
19 stay, if they stay on these doses of 15 to 20 of
20 oxycodone or higher doses of hydrocodone, they're
21 discharged on these higher dosages.

22 This medication can be used as a bridge

1 either from the operating room until they're able
2 to go onto their oral medications that they can
3 then take home or as a bridge from the IV to the
4 sublingual, and then to the oral as they're able to
5 go home. As they've talked about earlier today,
6 people do not go home on this medication.

7 DSUVIA is a medication that's able to be
8 easily administered. It's sublingually given. It
9 really is designed to minimize diversion, and we've
10 seen this with the ability to avoid intravenous
11 medications, as they're more easily able to divert
12 in this type of a medication. It's rapidly reduced
13 patients moderate to severe pain in the clinical
14 trials and showed that these patients tolerated
15 this medication quite well, even though the elderly
16 patients tolerated it well and those with impaired
17 renal function.

18 Additionally, the safety profile and adverse
19 events seen in these clinical trials was consistent
20 with what we've seen in other opioids. So this is
21 not providing any new adverse events that we
22 haven't seen in other opioid medications. These

1 results illustrate DSUVIA not only effective in
2 reducing pain but safe in a way that has minimal
3 adverse effects.

4 In conclusion, I believe that DSUVIA is a
5 medication that could provide effective pain relief
6 but also with minimal adverse events as long as a
7 risk evaluation and mitigation strategy is employed
8 and patients are kept in a medically supervised
9 setting. Thank you very much.

10 DR. ZACHAROFF: Thank you. Will speaker
11 number 9 please step up to the podium, introduce
12 yourself, and for the record, please state your
13 name and any organization you are representing.

14 DR. WEBSTER: Hello again. I'm Lynn
15 Webster, vice president of scientific affairs for
16 PRA Health Sciences. I'm speaking only for myself
17 and have not been compensated for my time or
18 expenses. Also, I've not been involved in any
19 phase of DSUVIA's development.

20 There are two questions I would ask the
21 committee to consider today. First, is there a
22 need for an opioid with the characteristics of

1 DSUVIA? And second, is the safety profile of
2 DSUVIA acceptable? Regarding the need, everyone
3 recognizes there is a serious opioid crisis in the
4 United States. Many measures have been taken to
5 address the problem. Some efforts have resulted in
6 fewer opioids being prescribed. This is not
7 necessarily bad, but it has had or led to
8 unintended consequences.

9 Inadequately controlled acute pain can
10 increase the risk of chronic pain. Many academic
11 publications have reported that undertreated pain
12 increases the risk of dementia, memory loss, and
13 premature mortality. As an advocate for people in
14 pain, I want to see the most suffering among us
15 receive the compassionate care they deserve.

16 Because of the risks associated with
17 prescribing opioids, many physicians are choosing
18 not to treat their patients who have severe pain.
19 Even hospitals, pain is frequently undertreated. A
20 recent New England Journal of Medicine Commentary
21 by Dr. Eduardo Bruera from MD Anderson states that
22 in his institution, there's been serious shortages

1 of parenteral opioids necessary to provide relief
2 from cancer-related pain.

3 Unfortunately, his cancer center is not an
4 exception. There's a national shortage of
5 parenteral opioids. We heard this yesterday at
6 this meeting, particularly in cancer centers as a
7 direct result of government interventions to curb
8 the opioid crisis. Providers are now often forced
9 to find alternative means to meet the needs of
10 their patients, and frequently, the options are
11 inadequate.

12 Parenteral opioids are desirable due to the
13 immediate and reliable analgesia. Many patients
14 requiring postoperative an palliative pain relief
15 are not able to take oral analgesics. DSUVIA is a
16 rapid onset, sublingual analgesic that is similar
17 to parenteral opioids in onset and avoids oral
18 ingestion. Therefore, DSUVIA could help fill an
19 unmet need.

20 The second consideration is regarding
21 safety. I'm quite familiar with sufentanil having
22 used it extensively in the operating room and in

1 labor and delivery for years as a practicing
2 anesthesiologist. I also used it off label with
3 intrathecal delivery systems for chronic pain.
4 It's a potent opioid that can provide clinical
5 benefits to the appropriate patients.

6 DSUVIA has inherent risks that are typical
7 of other opioids, including addiction and overdose
8 deaths. However, the context in which an opioid is
9 used in managed may be more important than the
10 inherent pharmacologic risks of a product.

11 In other words, we should ask the following
12 questions. For whom is the drug intended, and is
13 there a risk mitigation strategy to ensure the drug
14 is used properly? Who should be authorized to
15 prescribe the product? How would the prescribers
16 and those dispensing the drug be trained to ensure
17 the safest possible use? How can a patient be
18 prevented from taking more than intended?

19 Since diversion from well supervised
20 hospital settings is very uncommon for all opioids,
21 we can trust there will probably be systems in
22 place to mitigate diversion. So the major concern

1 with the product would be inappropriate use. This
2 morning, AcelRx stated that provider education is a
3 key component to their risk mitigation strategy to
4 ensure appropriate use.

5 Therefore, it would appear that with a
6 robust provider education program proposed by
7 AcelRx, DSUVIA could help fill an unmet need by the
8 shortage of parenteral opioids with minimal risk of
9 harm to patients and to society. Thank you for
10 your attention.

11 DR. ZACHAROFF: Thank you. Will speaker
12 number 10 please step up to the podium, introduce
13 yourself, and please state your name and any
14 organization you are representing for the record.

15 DR. SRINIVASAN: Hi. Thank you for your
16 opportunity to speak today. My name is Dr. Varuna
17 Srinivasan. I'm a physician with a masters of
18 public health from Johns Hopkins University. I'm a
19 senior fellow at the National Center for Health
20 Research, which analyzes scientific and medical
21 data to provide objective health information to
22 patients, health professionals, and policy makers.

1 We do not accept funding from drug and medical
2 device companies, so I have no conflicts of
3 interest.

4 We have strong concerns about the safety of
5 the drug in question today, sufentanil. First, we
6 are concerned that the level of pain relief
7 provided by sufentanil is not clinically
8 meaningful. Patients taking the drug had
9 statistically lower levels of pain than patients
10 taking placebo based on their SPID scores, but this
11 difference was so small, I would not consider it
12 helpful to my patients.

13 Just as important, there was no statistical
14 significant difference in how long it took for
15 patients to experience meaningful pain relief
16 between placebo and this drug that is supposedly
17 5 times more potent than fentanyl. If it really
18 were more effective than placebo, surely it would
19 work more quickly to relieve pain than the placebo.

20 The weak results are even more problematic
21 because there was only one pivotal phase 3 clinical
22 trial. We have an opioid epidemic, and it's

1 crucial that the FDA not approve opioids that are
2 not proven to work.

3 There is also limited diversity in the
4 clinical trials in terms of age, race, and clinical
5 conditions. Most of the study patients are white,
6 and many were under the age of 50. We would assume
7 that a wide variety of patients visit the ER or
8 undergo surgery, but that diversity is not
9 reflected in the study population. The sponsor
10 also failed to look older patients in trials of
11 sufentanil 30 microgram and extrapolated the data
12 from 15 microgram even though we know that pain
13 tends to increase with these.

14 In summary, this drug has not proven to have
15 a meaningful effect or impact on reducing pain in
16 postoperative settings. I respectfully urge you to
17 let the FDA know that the agency should require
18 better evidence of the efficacy of this drug. The
19 sponsor should submit more conclusive data to this
20 advisory committee before it can consider
21 recommending approval for sufentanil. Thank you.

22 DR. ZACHAROFF: Thank you. Just checking to

1 see if speaker 7 has arrived.

2 (No response.)

3 DR. ZACHAROFF: It doesn't appear so.

4 Okay. Then we have reached the conclusion
5 of the open public hearing session. The open
6 public hearing portion of this meeting has now
7 concluded and we will no longer take comments from
8 the audience. The committee will now turn its
9 attention to address the task at hand, the careful
10 consideration of the data before the committee as
11 well as the public comments made. We will ask
12 Dr. Hertz to provide us with the charge to the
13 committee.

14 **Charge to the Committee - Sharon Hertz**

15 DR. HERTZ: Thank you. This is Sharon
16 Hertz. Once again, you've heard a lot of
17 information this morning. You've heard about the
18 safety and efficacy data for DSUVIA, sufentanil
19 sublingual tablets in a 30-microgram dose for
20 management of moderate to severe acute pain, severe
21 enough to require an opioid analgesic for which
22 alternative treatments are inadequate in adult

1 patients in a medically supervised setting.

2 You've heard about some of the differences
3 of opinion between the agency and the sponsor. I
4 think onset of action was one of the big ones.
5 You've heard about the risk mitigation strategy
6 that's been proposed.

7 Now we're going to ask you to discuss each
8 of those things and tell us what you think about
9 the available efficacy data, safety data, and
10 whether you think the information from human
11 factors studies in the clinical trials inform how
12 to use the product safely and effectively, and also
13 whether the REMS can achieve what it's intended to,
14 which is to prevent the product from going home.
15 That's really the focus more than children in the
16 hospital. It's really more outside. I think we
17 got a little sidetracked.

18 We also want to hear if you think that this
19 product -- it would be the first sufentanil product
20 not used in the context of the OR, so what impact
21 that may have for some of the problems with abuse
22 and misuse. Then based on all of these points,

1 please let us know if you think this product should
2 be marketed, and as important as the vote is why
3 you've made your decision to support that vote.

4 Thank you for your time and consideration,
5 and back to you, Dr. Zacharoff.

6 **Questions to the Committee and Discussion**

7 DR. ZACHAROFF: Thank you, Dr. Hertz.

8 Just before we get to the questions, I would
9 like to urge the panel members that while we do
10 encourage discussion about the topics, we don't
11 want you to tell us what your vote is. We'll leave
12 that for the actual vote itself. So we're very
13 interested in engaging in discussion of the
14 questions as they arise.

15 We will now proceed with the questions to
16 the committee and panel discussions. I would like
17 to remind public observers that while this meeting
18 is open for public observation, public attendees
19 may not participate except at the specific request
20 of the panel.

21 Question 1 for discussion, discuss whether
22 the data are adequate to support a finding of

1 efficacy for sufentanil sublingual tablets
2 30 micrograms for the proposed indication, the
3 management of moderate to severe acute pain, severe
4 enough to require an opioid analgesic and for which
5 alternative treatments are inadequate in adult
6 patients in a medically supervised setting.

7 If there are no questions or comments
8 concerning the wording of the question, we will now
9 open the question to discussion by the panel.
10 Dr. Meisel?

11 DR. MEISEL: Steve Meisel with Fairview in
12 Minneapolis. I was really intrigued by this
13 product, but I think I'm disappointed with the data
14 because I don't think we have data to answer this
15 question. There are no comparative efficacy
16 studies with any other narcotic or non-narcotic
17 medication. We have no idea whether this drug
18 works as well as, or better than, or worse than
19 ibuprofen, acetaminophen, aspirin, or morphine. We
20 have placebo-controlled trials, but that's about
21 it.

22 The onset of action, the maximum onset of

1 action or the peak action is in an hour. That's
2 pretty slow for a drug that's supposed to be used
3 for really acute pain. There are some safety
4 concerns that go along with that we'll talk about
5 on the next question or two. But, boy, for a
6 situation where you have surgery and you're
7 expecting moderate to severe pain, and you've got a
8 drug that we have no idea whether or not it's as
9 good as, better than, or worse than any other
10 narcotic on the market because there's no data,
11 that concerns me.

12 I think the answer to this question is no.
13 I don't think the data are there to support or
14 refute. I mean, maybe it does. Maybe it is
15 effective, but the data presented today doesn't
16 address that one way or another.

17 DR. ZACHAROFF: Thank you. And just a
18 reminder, as we enter discussion, please identify
19 yourselves before your statement.

20 Dr. Fischer?

21 DR. FISCHER: Mike Fischer, Boston. I'll be
22 brief echoing on Steve's point. Looking at the

1 discussion question, there are two elements that
2 we're dealing with here. One is, is it severe
3 enough to require an opioid analgesic? And as was
4 pointed out, we certainly are dealing with
5 situations where there's pain that is severe enough
6 to be treated, but is it at a level where that
7 opioid analgesic's required?

8 It's hard to say. Certainly, it's clearly
9 better than placebo, but it's the alternative
10 treatments that are inadequate that really bugs me.
11 But we heard some really compelling anecdotal
12 descriptions of clinical scenarios. The ER patient
13 who is elderly, a burn patient; there are
14 situations where immediate IV access can be very
15 difficult. That's compelling anecdotally, and we
16 all can think of -- clinicians can think of cases
17 like that. But I didn't have a sense that that is
18 most frequent, and those weren't really the kinds
19 of patients about whom we saw data. We saw data
20 about the kinds of patients in who it's relatively
21 easy to get IV access.

22 So I feel like that alternative treatments

1 are an inadequate point. I have reservations about
2 whether that has been addressed adequately in the
3 data that we've been shown today.

4 DR. ZACHAROFF: Thank you. Dr. Litman?

5 DR. LITMAN: Thank you. Ron Litman,
6 Children's Hospital, Philadelphia and ISMP. I
7 apologize for not doing this earlier in relation to
8 these other questions. The FDA showed slide 16,
9 and I'm wondering if either the FDA or the sponsor
10 could give us more granular details about this time
11 to onset, time to meaningful pain relief, SAP 301.

12 DR. HERTZ: This is Sharon Hertz. We have a
13 very standard approach for determining the time to
14 onset, and that is we think the best approach is to
15 actually ask the patient to let us know when they
16 feel onset. Patients usually can't detect a
17 statistically significant difference in pain
18 curves, but they can tell us when they start to
19 feel an effect. So that would be the actual
20 clinical onset.

21 We do 2 stopwatches because the first one
22 can sometimes be pretty variable surprisingly not

1 as much with NSAIDS, but certainly with opioids.
2 And they're not quite sure. Maybe it's starting.
3 So that's why we start off with first perceptible,
4 but then what we really want to know is when
5 they're starting to get some real pain relief. So
6 that's why there's a second stopwatch.

7 DR. LITMAN: And the meaningful is the
8 second stopwatch.

9 DR. HERTZ: Yes. And that's the standard
10 that has been used for decades. As you all know,
11 we've been challenged to understand how to evaluate
12 pain and pain relief beyond actually asking
13 patients because people want some type of objective
14 measure. But pain is subjective, and meaningful
15 pain relief, the onset of pain relief is a
16 subjective concept that only the patient can answer
17 for themselves.

18 So that's why we use the double stopwatch
19 method, and that's why we select the time for
20 meaningful pain relief, the median time for
21 meaningful pain relief. And what that means is
22 there are going to be people for whom pain relief

1 is earlier and people for whom it's later. We
2 choose the median as the best estimate on this.

3 DR. LITMAN: For this drug, are those curves
4 available? I want to get a better idea. I'm
5 looking at -- the median to me, with a 95 percent
6 confidence intervals, is 42 to 72, which to me is
7 kind of like the same as an oral oxycodone,
8 approximately. But the range is really strange.
9 It's 4 minutes to 4 hours.

10 DR. HERTZ: Some people did not register an
11 onset. I suspect that kind of a number is some
12 type of error.

13 DR. LITMAN: No, of course. But I'm just
14 curious if there were curves associated with these
15 tables, so we can get a better graphical --

16 DR. HERTZ: We don't usually look at curves
17 for onset.

18 DR. LITMAN: Not onset but --

19 DR. HERTZ: I don't think we have --

20 DR LITMAN: I just think it would give us a
21 nice idea of the population distribution and what
22 their meaningful pain relief values were, if it's

1 available.

2 DR. HERTZ: I don't think we have it
3 prepared as a slide, so sorry about that.

4 DR. LITMAN: Okay. Thank you.

5 DR. ZACHAROFF: Thank you. Dr. Terman?

6 DR. TERMAN: Greg Terman from University of
7 Washington, Seattle. I do think that there's data
8 to support efficacy for pain in the data,
9 particularly if you combine the various studies,
10 including open label. I think the open-label
11 curves might give a bit of an indication that
12 people do seem to get better in terms of their
13 pain. It's not specifically the question you were
14 asking, but it does appear that people's pain can
15 improve.

16 The question is really does it fit in the
17 landscape for what we're lacking. As was mentioned
18 in the public comment period, we really are lacking
19 a nice sublingual to send home with people that
20 can't swallow so they don't have to be on IV
21 medications, something that for whatever reason,
22 their gut's really not working. And trying to find

1 a way to help those people would be really good.
2 And because of the REMS situation, in particular
3 this REMS, that won't happen with approval of this
4 drug. It will not be going home with people who
5 can't swallow.

6 The other hole in the landscape is something
7 fast acting, as I mentioned earlier, and that
8 really would be great. But what I'm seeing is that
9 people kind of get better after a couple of hours.
10 And in the IV comparison that was referenced by the
11 sponsor, IV morphine comparison with the PCA
12 sublingual sufentanil that was published, even
13 then, there's really no difference for a couple of
14 hours.

15 You look at the onset time, it wouldn't be
16 bad if it was similar to morphine onset. It's a
17 little less enthralling if it's similar to the
18 oxycodone, so that in an emergency situation where
19 you don't have an IV, maybe just give them
20 oxycodone. So I do think it's efficacious. I'm
21 just not sure it fills a niche, but I'm not telling
22 you my vote.

1 DR. ZACHAROFF: Thank you. I think I may be
2 the only one -- Mr. O'Brien, did you have something
3 you wanted to say?

4 MR. O'BRIEN: Yes. Again, it's always
5 depending on what the question is here. We found
6 from previous meetings, yesterday and whatever, to
7 say, okay, from a regulatory standpoint, you have
8 this standard where you have to show that in fact
9 the drug that's being put before is better than a
10 placebo. Well, the FDA tells me that in fact the
11 data is adequate to show that it is better than a
12 placebo. So from that perspective, I would say
13 yes.

14 The rest of the question says for which
15 there are no better alternative treatments, are
16 inadequate. I would agree with Dr. Meisel that as
17 I went through this, I kept on questioning the
18 population. I don't know if these patients really
19 needed what they got. It was not that clear to me
20 as I went through it that these patients really
21 need it. I don't know, but that wasn't a question
22 that I was asked.

1 I heard during the patient population that
2 there are in fact comparative drugs that may be
3 available with similar sublingual drugs, and may
4 not have the same delivery system, but sublingual.
5 I don't know that. I'm not a professional in that
6 area. I'm not a pharmacist or an anesthesiologist,
7 so I think that would be very important to know
8 whether or not -- because we weren't asked about
9 superiority to a comparator drug. We were just
10 asked does the data show that it supports.

11 So I'm told the data supports. I'm not
12 quite sure it's needed. I think there are clearly
13 needs. As I expressed anecdotally, I can
14 definitely see -- personally speaking, when I was
15 in that ambulance, if I could have got that
16 sublingual drug, I would have greatly appreciated
17 it. It was needed. They couldn't get an IV in.
18 And you didn't have to worry about what my
19 indication was because I was balled up in agony and
20 pain, grunting like an animal. And when I stopped
21 grunting like an animal, you knew it was working,
22 in that particular case.

1 Again, it depends on what the FDA is asking
2 the question for. I accept that they tell us that
3 the data shows that it is better than the placebo,
4 but I have questions about that.

5 DR. HERTZ: This is Sharon Hertz. Can I
6 just clarify? Our standard is not better than
7 placebo for efficacy. Our standard for an
8 analgesic efficacy study is to show that there is
9 efficacy that is superior to some comparator. And
10 the reason for that is if you simply look to see in
11 an analgesic study, without what we call downside
12 sensitivity -- if you just look to see if something
13 is the same as a comparator, we don't know if that
14 means both work or both don't work.

15 So what we would consider ideal would be to
16 have a placebo and an active comparator, and we
17 often discuss this with companies. So we may not
18 be in a position to impose a requirement of an
19 active comparator, but there's no reason why a
20 sponsor cannot include that in one or several
21 studies to determine how the product is performing
22 relative to other things.

1 MR. O'BRIEN: Thank you very much for that
2 clarification. In that case, I think it would be
3 very important and very useful for the sponsor to
4 take that next step and show that, in fact, it is
5 better than a comparator because they have a great
6 delivery system that I'm very much in favor of, but
7 I think the other questions have to be answered as
8 well.

9 DR. ZACHAROFF: Dr. Zeltzer?

10 DR. ZELTZER: Lonnie Zeltzer, UCLA, Los
11 Angeles. First, I think your comment, Mr. O'Brien,
12 without a comparator -- I mean, we know that it
13 seems better than placebo. We don't know if it's
14 better than what else is out there for acute,
15 moderate to severe pain. I guess the very narrow
16 area in which I don't think we have other agents is
17 in the acute setting of the emergency department or
18 in another acute setting where an oral agent cannot
19 be tolerated for various reasons and while
20 attempting to get an IV in, especially if it's
21 difficult to get an IV in an individual.

22 So one has a very smaller area where I do

1 see a need that we don't have right now, which is a
2 smaller window than what is being asked for here.

3 As was mentioned, it would be nice to see a
4 comparative study of morphine, or dilaudid, or some
5 other agent, oxycodone, acetaminophen. But for
6 those who cannot tolerate an oral agent or while
7 waiting for an IV, I don't know another comparative
8 that we have at this point.

9 DR. ZACHAROFF: Thank you. Dr. Kaye?

10 DR. KAYE: Alan Kaye, LSU. I think it's
11 efficacious, and I think there is a niche beyond
12 placebo for the delays in oral onset. And I think
13 that there is a niche for IV for the reasons a
14 number of people have mentioned, which is you can't
15 always get an IV and it can be problematic and
16 delayed.

17 So I think the way I read this question is
18 that, yes, it's efficacious and that it serves a
19 purpose where alternative treatments are inadequate
20 in adult patients in a medically supervised
21 setting.

22 DR. ZACHAROFF: Just lastly, before I

1 summarize, my only point of discussion for this
2 question is the last three words in the question,
3 and that's "medically supervised setting." We had
4 some discussion earlier in the day about what the
5 definition was. We heard some thoughts from the
6 sponsors about a willingness to possibly narrow in
7 the scope of that.

8 For me, I think there probably has been
9 enough data presented to support efficacy in a
10 hospital setting. Medically supervised setting
11 means so many different things to me that I could
12 imagine we could end up in surgicenters, and
13 walk-in clinics, and anyplace else. If I'm
14 thinking about this medication as one that might
15 potentially be administered to a patient,
16 readministered to a patient over some period of
17 time, a medically supervised setting just doesn't
18 cut it for me.

19 So I haven't been satisfied in the scope of
20 the definition as presented that the data was
21 adequate because it doesn't say hospital setting.

22 DR. PALMER: Could I address the fact that

1 we have active comparator data?

2 DR. HERTZ: You can't start presenting new
3 data now. You did not submit active,
4 well-controlled, with downside sensitivity data for
5 us to review here.

6 DR. PALMER: It's Zalviso active comparator
7 data that's on file for Zalviso with the NDA.

8 DR. HERTZ: What would you like us to do
9 with that now?

10 DR. PALMER: I just have one slide.

11 DR. HERTZ: Sure.

12 DR. PALMER: Thank you. So just to clarify,
13 our first product was Zalviso, and we actually did
14 a head-to-head comparator against IV morphine.
15 I'll just quickly cover this. I'm talking about
16 pain intensity difference, so that means a positive
17 number means better. The pain intensity difference
18 from placebo was greater as it goes up.

19 You can see here that Zalviso from a
20 sublingual is 177 patients. Sublingual sufentanil
21 had a more rapid pain intensity difference from
22 baseline than morphine. It eventually caught up;

1 morphine caught up at about hour 6. And this is
2 because it's not as lipophilic as sufentanil is.
3 After we already knew we were faster than IV
4 morphine, when we did the DSUVIA studies, we did
5 not bother with a comparator because we had already
6 demonstrated this, so I apologize.

7 DR. HERTZ: Dr. Palmer, this study I believe
8 also had quite a bit of rescue in the Zalviso arm,
9 and we're trying to confirm. Was this a blinded
10 study?

11 DR. PALMER: No. This is open label, and
12 there was very little rescue. There was only
13 2 milligrams in 48 hours.

14 DR. HERTZ: And what was the patient
15 population? See, we don't have the information
16 right now to adequately understand the conditions.
17 We don't know the number of Zalviso doses. We
18 don't know if the ultimate amount that accumulated
19 over time was comparable to what's possible with
20 DSUVIA based on the current dosing paradigm. We
21 know that the accumulation in Zalviso was
22 potentially much higher than the accumulation in

1 DSUVIA.

2 So let me thank you for presenting this, but
3 I don't want it to go without saying that we don't
4 have details for this study, the patient
5 population, timing of the study. I mean, there's
6 just a lot of information that isn't conveyed in a
7 single slide.

8 DR. PALMER: This is in our briefing book.
9 Sorry. This is not new data. This is in our
10 briefing book for this NDA. We submitted this
11 data. We also submitted oxygen saturation data
12 showing that sublingual sufentanil has fewer
13 patients with oxygen saturation below 95 than IV
14 morphine.

15 DR. HERTZ: That was with Zalviso, correct?

16 DR. PALMER: Yes.

17 DR. HERTZ: In a different setting,
18 different patient population.

19 DR. PALMER: Correct.

20 DR. HERTZ: Okay.

21 MR. O'BRIEN: I just want to make sure it is
22 in your briefing book. I just want to be clear.

1 DR. ZACHAROFF: Thank you. And just as a
2 reminder, no disrespect intended, but we're going
3 to try to avoid that scenario if we can.

4 We do have one more comment for discussion,
5 and that is Dr. Shoben.

6 DR. SHOBNEN: Abby Shoben. Before all that,
7 I'll just go ahead and comment and say that
8 efficacy for me was clearly demonstrated. I agree
9 with Dr. Kaye's point. And I don't actually think
10 that we need an active comparator here in part
11 because it's such a novel sort of delivery
12 mechanism, and it's a potentially different patient
13 population, proving that it's superior to placebo,
14 which I think the data clearly show. It was enough
15 for me.

16 Unlike situations where you have similar
17 delivery mechanisms and it's a more obvious
18 comparator, it was not needed in this setting for
19 me, and it should be up to the physicians to figure
20 out which ones they wanted to use for the patients
21 in the future.

22 DR. ZACHAROFF: Thank you. Just to

1 summarize perspectives on the panel with respect to
2 efficacy, some of us felt that the data may not
3 necessarily be sufficient for us. Others felt that
4 the novel delivery method, as we just heard, may
5 not necessarily preclude the need for a comparison.

6 Some panel members felt that there might be
7 an issue with respect to onset of action compared
8 to other modalities that are out there, but this
9 could very much be possibly compelling in patients
10 where IV access is an issue.

11 We did hear from people that IV access
12 doesn't necessarily mean that there's inadequate
13 alternative treatments, but nonetheless, we did
14 hear that in patients where there is a situation
15 where IV access may not be obtainable, or people
16 may not be able to tolerate oral medications, this
17 medication could potentially be of value based on
18 the data presented. We did hear feelings that a
19 sublingual solution to opioid analgesia does meet
20 an unmet need. And as we heard me state, a
21 medically supervised setting is something that's
22 unclear.

1 If there's anything I didn't capture, please
2 let me know now.

3 (No response.)

4 DR. ZACHAROFF: Okay. If there are no
5 further questions, we will -- Dr. Meisel?

6 DR. MEISEL: Steven Meisel from Fairview.
7 Just one additional efficacy comment, and that is
8 this is a fixed dose. U The 85-year-old grandma and
9 the 350-pound linebacker are probably going to need
10 different doses. The sponsor says, well, in those
11 cases, yes, that's why we allow the dose to be
12 given every hour. But that then is going to
13 further delay the efficacy for people who need
14 larger doses.

15 To me, that's an additional concern. I
16 can't give 60 micrograms right away; I have to give
17 30 and wait an hour for the person who needs more.
18 To me, I understand why it's a fixed dose. I
19 understand the rationale behind that. But to me
20 there's a safety concern with that, but there's
21 also an efficacy concern, and that is the people
22 who need higher doses have to wait an hour and let

1 it accumulate and maybe even get a third dose at
2 hour 3 and let that accumulate. That to me is a
3 significant efficacy concern.

4 DR. ZACHAROFF: Thank you for that addition,
5 and that probably goes in line with what I
6 mentioned earlier on in the day about lack of
7 ability to titrate.

8 We will move on to question 2. Based on the
9 available safety data, discuss any concerns that
10 you may have about the safety profile of sufentanil
11 sublingual tablets, 30 micrograms. If there are no
12 questions or comments concerning the word of this
13 question, we will now open the question to
14 discussion.

15 Dr. Higgins?

16 DR. HIGGINS: I see no observed relationship
17 between increased doses of the drug and AEs,
18 however, I do still remain concerned about older
19 adults and their decreased clearance with age and
20 several other factors that make them a very
21 vulnerable population that I feel hasn't been
22 adequately studied to my satisfaction and do want

1 to say that I think they need extra care, and
2 protection, and attention. And I would hope that
3 this could be conveyed in some way, perhaps through
4 labeling, if and when we approve the drug.

5 DR. ZACHAROFF: Thank you. Dr. Meisel?

6 DR. MEISEL: I agree with Dr. Higgins'
7 comments about the elderly. In fact, the data are
8 so weak in the elderly that if this drug were
9 approved, I would think it would have to be limited
10 to people under the age of 65 because there just
11 isn't any data whatsoever in that space and the
12 risks there are pretty high.

13 A couple of other points. A lot has been
14 made about the fact that you don't have to have an
15 IV line for this drug because it's sublingual.
16 Well, no IV line also means that if you need to
17 give rescue naloxone, you have no IV line. Now,
18 there are other ways of giving naloxone, but it
19 doesn't work as fast or as well as, as it does IV.

20 So you sort of take the good with the bad
21 with this. And if somebody needs to be rescued and
22 there is no IV line, that's going to be a serious

1 problem. That's a concern that I've got with this
2 drug in the way that it's being proposed to be
3 used, and I think we need to be cognizant of that.

4 The other point about safety here, as I
5 mentioned before, because the 30 mgs may not be
6 effective, the instructions for use will say wait
7 an hour, but the real world will say that somebody
8 is going to give rescue or something before that,
9 at 15 minutes, at 30 minutes, or something, or
10 they'll give another dose of this despite the fact
11 that you're supposed to wait an hour.

12 The real world is the real world. That's
13 what's going to happen. And we're going to end up
14 with multiple narcotics on board, lots of dose
15 stacking. That will happen with that, and I don't
16 think that's been well elucidated and well
17 characterized, but I think it's a reality that we
18 need to recognize that is unique for this because
19 of its delivery system and because of the fixed
20 dose and the 1-hour dosing interval. So those are
21 the additional safety concerns that I've got.

22 DR. ZACHAROFF: Thank you. Dr. Litman?

1 DR. LITMAN: Thank you. Ron Litman. I
2 agree with most of what's been said about the
3 risks, and just from the totality of the data
4 presented, I don't think that there's much of a
5 risk, but mainly because I don't think it's just
6 that potent of a drug. I think it's probably about
7 the same as taking an oral oxycodone, although
8 obviously without the oral has disadvantages if you
9 can't swallow or if you've recently eaten.

10 That's one point. The other one, maybe I
11 should have said this in the efficacy section.
12 We've been talking a lot about anesthesia and
13 post-op. I really don't see a role for this drug
14 in the anesthesia peri-operative environment. I
15 really can't think of a situation where an
16 anesthesiologist would need this.

17 Honestly, there are very few adults, if any,
18 that don't have an ivy coming out of surgery, a
19 pre-op. I mean if you don't have an IV coming out
20 of surgery. Pre-op, if you don't have an IV, that
21 means you've come from home. I don't know, but
22 you'd have to speculate on some unique painful

1 condition.

2 So it's really not a peri-operative drug.
3 It would be very useful for the other scenarios we
4 talked about like emergency room or in the
5 military, but as far as safety goes, I haven't seen
6 really much to make me very concerned. And
7 although I agree, Dr. Higgins, about the elderly, I
8 am comforted knowing that we give a lot more
9 powerful drugs to the elderly through their IV in
10 these same situations. So I don't think it's any
11 more dangerous than that at all.

12 DR. ZACHAROFF: Ms. Willacy?

13 MS. WILLACY: Jacqueline Willacy. From a
14 nursing perspective, we talk about stacking those
15 every hour. It's very taxing on a nurse. You have
16 4 patients in ER or maybe on another unit where you
17 have several patients, and if you have to go to
18 give this medication on an hourly basis, it's not
19 going to be effective because it's just a time
20 timeframe where you're taking care of other
21 patients. This is almost like it's a one-to-one
22 patient because you're going back to the Omnicell

1 to get this medication to deliver this medication.

2 DR. ZACHAROFF: Thank you. Any other
3 comments with respect to the available safety data
4 and concerns we might have?

5 (No response.)

6 DR. ZACHAROFF: Okay. To summarize what I
7 heard and make sure I captured it adequately, there
8 was a sense that it's possible there might be
9 insufficient data in patients over the age of 65
10 with respect to the data that was presented today.
11 We heard that poor IV access might be a problem,
12 especially if naloxone is necessary, which is
13 conceivable that it will occur.

14 I was always taught that as an
15 anesthesiologist, when you give a drug, you need to
16 know how to take it back. I did have some concern
17 from the safety perspective about a patient with a
18 long bone fracture being given a sublingual
19 medication and then being sent off to x-ray with no
20 intravenous in and no ability to give an antagonist
21 if it was needed.

22 When I think of people who are on opioid

1 therapy, I usually think of a 3 cc syringe, a
2 needle, and an ampoule of Narcan nearby. So the
3 fact of the matter is that if this is truly a
4 bridge, as we heard some people mention in the open
5 public hearing, then at best it's a bridge to being
6 able to get an IV in after you've got pain
7 controlled, not give pain control and then never
8 have to put an IV in. So that was a safety concern
9 of mine, which I agreed with Dr. Meisel.

10 Definitely we heard from a few people about
11 the real-world issue of dose stacking and not
12 knowing what people will do with patients who still
13 have pain, because we do know that institutions get
14 rated based on how satisfied patients were with
15 respect to their pain management, and that ends up
16 being a financial penalty if they don't get good
17 HCAHPS survey scores. So in all likelihood, there
18 is a concern, and we didn't necessarily see data
19 about what will happen if patients are given
20 medications, if this drug is ineffective.

21 Then lastly, and I'm very glad we heard
22 this, about what the practicality might be of the

1 logistics of giving this medication on an hourly
2 basis for a nurse, not only thinking about having
3 to go to a patient's room to readminister this
4 every hour, but also noting when it was actually
5 administered, if the nurse is moving from patient
6 to patient to patient, it might not actually get
7 charted that it was given until some period of time
8 after it was given, and that could throw off how
9 well the pain is managed.

10 Did I leave anything out?

11 (No response.)

12 DR. ZACHAROFF: Okay. Good. Thank you.

13 So we will move on to the next question,
14 question 3. Discuss whether data from the human
15 factors studies and the clinical trials support the
16 safe and effective use of the proposed product
17 administered by healthcare professionals in
18 certified settings such as hospitals, emergency
19 departments, and surgical centers. In your
20 discussion, consider whether the REMS proposed by
21 FDA can be expected to mitigate the risks
22 associated with dropped sufentanil tablets and

1 including the risk of accidental exposure.

2 Please take a minute to look at that lengthy
3 question because I'm going to ask you if there are
4 any questions or comments concerning --

5 MALE VOICE: Is that proposed by FDA
6 [inaudible - off mic].

7 DR. ZACHAROFF: According to the wording of
8 this question, it's REMS whims proposed by FDA.

9 Any other questions or comments concerning
10 the wording of this question before we move to
11 discussion?

12 (No response.)

13 DR. ZACHAROFF: Okay. Then we will now move
14 to open the question to discussion. Dr. Warholak?

15 DR. WARHOLAK: Terri Warholak from
16 University of Arizona. I really liked the REMS
17 suggestions that the FDA made. and I feel like
18 there were really good changes made to the
19 instructions and to the plan. One of the things
20 that I thought would be helpful for the future,
21 especially since this involves the device, it might
22 be really nice to give a placebo package to each of

1 the committee members so that we could play with
2 it.

3 One of the things that I've found doing
4 human factors training is everything seems simple
5 until you do it. For example, even
6 situations -- like I have a friend who bought a new
7 refrigerator, and they were reading reviews online,
8 and one of the reviews said that the ice cubes were
9 hard to catch in your cup. And I thought, "Who
10 can't catch an ice cube in a cup?" But it was so
11 interesting because when you put the cup under the
12 ice cube dispenser, it shot out and not down.

13 So it would've been really nice to just play
14 around with one of the placebos before we came here
15 so that we can have an idea of exactly how big it
16 is and what some of the issues might be.

17 DR. ZACHAROFF: Thank you. Ms. Phillips?

18 MS. SHAW PHILLIPS: I also support the
19 suggested changes to the REMS program that the FDA
20 is recommending, particularly broadening the reach
21 of the education to all personnel that really need
22 to get it. I think in the grand scheme of things,

1 the issue with dropped tablets not being detected,
2 particularly since the patient can sense the tablet
3 or taste the tablet, in 80 percent of the cases is
4 not as big an issue. And as was discussed with the
5 meticulousness in the healthcare setting, it's much
6 less likely for a dropped tablet to go unnoticed
7 and get accidentally consumed.

8 I think the greater concern is the
9 benefit-risk assessment, the targeted group of
10 patients that really would benefit more from this,
11 looking at the efficacy in the context of the REMS
12 program that's needed, and also just being another
13 fun drug of abuse that we would need to protect for
14 getting outside of hospitals.

15 DR. ZACHAROFF: Thank you. Dr. Litman?

16 DR. LITMAN: Thanks. Ron Litman. I don't
17 have a lot of concerns about the human factors. I
18 don't have a great deal of confidence that the
19 REMS, at least in this, will make a difference.
20 However, the stuff about the RADARS that we talked
21 about this morning is really interesting. And if
22 Dr. Dart sees one of these come up on his

1 radar -- that's kind of a pun -- then that would be
2 alarming. So that would be helpful. Yes, I don't
3 envision any other human factors problems.

4 DR. ZACHAROFF: Thank you. Dr. Fischer?

5 DR. FISCHER: I agree with some of what
6 Dr. Litman was saying. The REMS, I'm not totally
7 convinced that the scope of the education that was
8 proposed either by the applicant or FDA is that
9 realistic, but was very reassured and actually
10 thought it was commendable to do a very real-world
11 human factors study in which people, it sounds
12 like, may well not have read the directions but
13 were still able to figure out how to use the device
14 and not lose the pills. And that's quite
15 reassuring to me that in -- it was only 45, as
16 someone pointed out. But still in real-world use,
17 the human factors concern is less so.

18 I think as it was well pointed out in the
19 comments, we can come up with a story for a dropped
20 pill, and I can understand the concern because one
21 case like that could be incredibly problematic.
22 But it seems like such a low probability that it

1 does not strike me as a reason to jump in the way
2 of this kind of delivery system.

3 DR. ZACHAROFF: Thank you. Dr. Meisel?

4 DR. MEISEL: Well, I too have a few
5 concerns. I do like the suggestion that, not only
6 for this product but for other products before
7 these committees where there's a delivery device
8 you certainly need to get your hands on to get a
9 feel for it, the hands-on is a lot better than the
10 photos and we should be considering that in the
11 future.

12 The one concern that I did have, and it was
13 in the applicant's portion of the REMS to require
14 that every hospital prospectively educate every
15 nurse who may be using this product before they use
16 it. I'm in an organization that's got 32,000
17 employees over 11 hospitals. I can't get my head
18 around a system whereby I could guarantee that were
19 to happen. We have nurses coming and going all the
20 time with new hires and what-have-you with a
21 million things they have to learn about how to run
22 the electronic health record to do their timecards

1 to everything else. To try to throw this into it
2 would be nothing more than a paper exercise and
3 would be highly ineffective.

4 Now, the real-time stuff, the once in a
5 while that you've got to use it, maybe this
6 particular ED is going to use it a lot, so you're
7 going to do some just-in-time training in your ED,
8 that's a different scenario. But to try to come up
9 with a system whereby you're prospectively
10 educating every nurse who may have to use this just
11 in case they do, I don't think that's practical.

12 DR. ZACHAROFF: Thank you. Mr. O'Brien?

13 MR. O'BRIEN: I commend the FDA on its
14 efforts in terms of the human factors. I think the
15 REMS portion does a good job. I would like to see
16 it. And as I asked, I think a sample of the
17 product would be very helpful for making decisions
18 like that, even despite photographs.

19 I think that it's not isolated. I think the
20 REMS plus with the sponsor indicating they are
21 going to do the training -- and yes, there are a
22 lot of things that hospitals and others have to do,

1 but we've got a major tragic epidemic on our hands
2 here, and I would hope that any institution would
3 understand that delivery of an opioid requires
4 priority. So you're going to have to lift that up
5 to make sure the people who are going to touch
6 this, who are going to deliver it, do in fact get
7 the training that they need in order to do that.
8 Whether it's considered or perceived to be
9 realistic or not, it's going to be required to do
10 that.

11 So I think the hospital and the sponsor
12 living up to their commitments to do training, plus
13 with the REMS, I think the three of them gives us a
14 tool of control that is reasonable in terms of
15 mitigating the risks that are there.

16 DR. ZACHAROFF: Thank you. Dr. Higgins, did
17 you have something to say?

18 DR. HIGGINS: Dr. Meisel stole my thunder.

19 DR. MEISEL: I'm sorry.

20 DR. ZACHAROFF: I'll just throw in my
21 comment that I agree. I think the FDA is to be
22 commended about doing the human factor evaluation.

1 And considering actually how a product like this
2 would be used, I also very much, from a safe and
3 effective use perspective, like the wording of
4 hospitals, emergency departments, and surgical
5 centers because that much more clearly defines
6 where this medication might be used safely and
7 effectively as opposed to the nebulous medically
8 supervised setting wording.

9 Dr. Fischer, did you have something else?

10 DR. FISCHER: I think Greg.

11 DR. ZACHAROFF: Okay. Dr. Terman?

12 DR. TERMAN: Greg Terman from University of
13 Washington in Seattle. I think that there's been a
14 lot of evidence that this is very similar in terms
15 of risks to other opioids. And with this REMS, I
16 would say that it's even more safe than most other
17 opiates used in the hospital.

18 I will admit that I was concerned about the
19 hourly possibility of nurses having to go in and
20 give multiple doses when in fact they've got lots
21 of other patients to take care of, but nurses can
22 be trained really well. I started when PCAs were

1 just coming into the hospital and epidurals have
2 come into the hospitals. And although I don't see
3 the niche for this particular product in the same
4 way, the human factors study demonstrated that even
5 with the instructions on the package, people can
6 know what to do.

7 Although they're supposed to also be taught,
8 it may be rare enough they'll be looking at those
9 packages. But it sounded like even in damaged
10 packages, after a little bit of experience in the
11 human factors trial, people stopped looking at the
12 packages and were able to do it just fine. So I
13 think that the REMS really limit use perhaps
14 appropriately but certainly safely.

15 DR. ZACHAROFF: Thank you. If there are no
16 more comments or discussion, just a summary of what
17 I captured. We heard from a number of people, it
18 would have been nice to see the product just to get
19 an idea of what it looked like, how it felt, and
20 how small the pill actually was. We heard positive
21 feedback by and large about the FDA proposed REMS,
22 and we also heard concern that if this medication

1 did end up showing up in RADARS data, that that
2 would be very concerning, indeed.

3 We heard positive feedback, almost
4 universally, about the human factor evaluation that
5 was done by the FDA, and we also heard that it
6 might not be practical to train every single person
7 in an institution who might be tasked with covering
8 the patient or needing to care for a patient who
9 might need to get a medication like this and that
10 that could be challenging.

11 We heard that, by and large, most people
12 felt that the risks of this particular opioid
13 medication are probably in line with or less than
14 those with other similar opioid medications. Then
15 lastly, that education might not end up being a
16 barrier based on the data provided that people were
17 able to not read the directions and still end up
18 giving the medication appropriately.

19 Did I get it?

20 (No response.)

21 DR. ZACHAROFF: Okay. So I'm taking this to
22 mean that there are no further questions or

1 comments regarding this or other questions that
2 we've addressed.

3 (No response.)

4 DR. ZACHAROFF: So then we will in a
5 moment -- I'm sorry. We will tackle question 4.
6 Discuss any concerns you may have regarding the
7 abuse or misuse of sufentanil sublingual tablets
8 and whether, based on the available data, the
9 benefits to patients are expected to outweigh
10 public health risks as they relate to abuse,
11 misuse, and accidental exposure.

12 So just take a moment to look at the
13 question. Let me know if there are any questions
14 or comments regarding the wording of this question.

15 (No response.)

16 DR. ZACHAROFF: Okay. Then we will now open
17 the question to discussion. Ms. Phillips?

18 MS. SHAW PHILLIPS: I think in terms of
19 abuse, we've got the same concerns we would have
20 with any other Schedule II substance that's in the
21 hospital, so that's not my greatest area of
22 concern. I think the area where I'm really toying

1 is the misuse, and thinking from a formulary
2 perspective in our health system, really thinking
3 about it potentially being used in areas where
4 there's not enough good evidence that it's a
5 suitable alternative or better alternative.

6 So again, I don't see this in a post-op
7 setting. And as an IRB chair, I'm looking at how
8 difficult it would be to do the studies that we
9 would really need to show if it has a niche and a
10 true public health benefit, which again is in that
11 immediate first-dose situation when you're trying
12 to treat somebody for initial pain management, and
13 you don't have access to the IV.

14 I think that would be a challenging study to
15 do without a community consent design or something
16 like that, but that would be the next thing that I
17 would be asking for to help weigh those things in a
18 little bit more detail.

19 DR. ZACHAROFF: Thank you. Dr. Kaye?

20 DR. KAYE: Alan Kaye from LSU. I think the
21 risk of abuse in the setting that it's been
22 described is rather low, and I think that the

1 benefits largely outweigh the risks. It will find
2 its own niche such as in settings like the
3 emergency room and perhaps in palliative care,
4 which we didn't really talk about today. But I do
5 think that, largely, the benefits would outweigh
6 the public health risks for abuse, misuse, and
7 accidental exposure.

8 DR. ZACHAROFF: Thank you. Dr. Meisel?

9 DR. MEISEL: I too am not overly concerned
10 about the abuse issues with this particular
11 product. All opioids can be abused, and one will
12 no doubt will be. The one unique feature about
13 this that may make it just a little bit unique in
14 this space of a hospital for somebody who wants to
15 divert is that it is a tiny tablet. It's readily a
16 dissolvable. Some nurse pretends to give it to a
17 patient and then pockets that, and then puts it
18 into a little bit of water or something, and
19 nobody's the wiser.

20 I could see that happening. Will that
21 happen commonly? Probably not. Will it happen to
22 the extent that that's greater than other opioid

1 diversions? Probably not. But it's a unique way
2 of diverting that probably doesn't exist with some
3 of the other products. Again, I'm not overly
4 concerned about it, but I think we just have to
5 acknowledge that that potential is there.

6 I do agree that there's more of a risk of
7 misuse than there is of abuse. Once this product
8 is available, people will find all sorts of unique
9 ways deciding to use it beyond labeling. There
10 will be indications that nobody has dreamed up
11 before; that even today, the sponsor would say, no,
12 don't do it, people will find a way of doing it.
13 And that will end up with all sorts of unintended
14 consequences.

15 Now, that isn't a factor for approval or
16 disapproval, but I think it's something we have to
17 acknowledge that all drugs wind up being used off
18 label, and when you have a drug as potent as
19 sufentanil, the consequences of that can be very
20 significant.

21 DR. ZACHAROFF: Thank you. Dr. Litman?

22 DR. LITMAN: Thank you. Ron Litman. I am

1 not overwhelmed with the usefulness of this drug,
2 however, I do believe that its benefits outweigh
3 the risks based on its unique ability to be used
4 sublingually. There are many questions still to be
5 answered. Is this just as good as Motrin? It
6 might be or there are other sublingual opioids that
7 are to be used, and I would ask the FDA to
8 carefully consider the difference between them.

9 So my guess, although I don't know the data,
10 is it's a sublingual form of fentanyl. If this is
11 really an unmet need that you need something in the
12 emergency room to treat somebody before you get an
13 IV in, well, there are a couple different forms of
14 sublingual fentanyl or buccal. My guess is that
15 Sufenta is less potent than those, and it might be
16 safer, although not as effective.

17 So those are the kinds of things I would
18 weigh. But because I don't see this as a public
19 health risk or a safety issue, I do think its
20 marginal benefits outweigh the risks.

21 DR. ZACHAROFF: Dr. Shoben?

22 DR. SHOBNEN: I would agree with what's been

1 said, that as it's currently set up with the REMS
2 in keeping it in hospital settings, that the risk
3 for public health, unintended abuse, misuse, and
4 accidental exposure risks are very minimal. I
5 would stress that that's very much based on the
6 assumption that it would stay in the hospital
7 setting. Kicking it out to an in-home kind of
8 place would both dramatically increase the risk of
9 accidental exposure and potentially abuse since
10 it's such an easily absorbed,
11 potentially very abusable kind of delivery device.

12 DR. ZACHAROFF: Thank you. So to summarize,
13 just to make sure I captured everything, it might
14 actually be difficult to determine what the public
15 health risk might be comparing it to benefit based
16 on the fact that it's likely to be used in an
17 institutional setting. It will likely find a
18 clinical home.

19 In the context of that clinical setting,
20 wherever it ends up being used, whether it's the
21 emergency room or some other place in a hospital
22 setting, we heard most members feel it's not likely

1 to increase the risk of aberrant behavior; that's
2 despite the fact that we can always expect that
3 that diversion is going to happen, and somehow or
4 other, one way or another, somebody's going to
5 figure out a way to get their hands on this
6 medication and abuse it.

7 We thoughtfully heard that, actually, it
8 might be the risk of misuse that may be the
9 challenge more than abuse or accidental exposure
10 because of the fact that people might still
11 experience breakthrough pain and people might give
12 it more frequently than they're supposed to. And
13 then we heard emphasis on the fact that risk of
14 abuse and misuse is probably low if it stays where
15 it's intended to stay based on the discussion we
16 have today.

17 Mr. O'Brien, did you have something to say?

18 MR. O'BRIEN: I do. Thank you. Sorry.
19 From my perspective, in looking at it from what
20 I've seen, I would almost say that I think the
21 abuse particularly, it's probably safer. It's less
22 tending. And I say that from actually being a

1 former director of white collar crime and director
2 of audit in the sense that when you look at the
3 human factor, you know how to package. It only has
4 one unit in there, so it only has a very limited
5 amount as opposed to stealing a bottle or something
6 else where I'm going to get 100 to 200. Now I have
7 to get a packet. I have to open up that packet. I
8 have to take that out. I have to use it
9 sublingually.

10 There are a lot of factors there that to me
11 would seem to mitigate the abuse as compared to
12 something else that I could get. If I'm going to
13 spend my time and energy, I would steal something
14 else to take that. So it would seem to be less
15 than that.

16 I do see that for the targeted population.
17 I don't see it myself. As I said, I don't think in
18 the spine community -- I don't see it for me. I
19 don't see how that would apply to that. I do see,
20 in the case that I had mentioned, my own specific
21 case in the ambulance and others that I've seen
22 that are in acute pain, that if it's immediate, and

1 it's faster, and it's sublingual when they can't do
2 it -- I do have caution -- I understand the need to
3 keep it within the hospital, but I do think about
4 our soldiers, and I do think about the battlefield,
5 and I do think about the opportunity there that was
6 expressed. And I think that's a very real need.

7 We heard from southern California very
8 specific numbers in terms of 2600 people that come
9 in, which is a third of those are over 65 and half
10 of those can't use IVs. So there is a very real
11 population that it appears for which there is a
12 need and that this would apply. I have to rely on
13 a lot of things for the doctors to do what they're
14 going to do and apply. And sometimes that goes way
15 off label and sometimes it doesn't, like everything
16 else.

17 But it seems to me like there has been a
18 true targeted needs that has been expressed for a
19 certain population that's here, that this would
20 provide -- this new novel delivery system would
21 provide and answer that need. So from that
22 perspective, I think the benefit overrules the

1 risk.

2 DR. ZACHAROFF: Ms. Phillips?

3 MS. SHAW PHILLIPS: I did want to follow up
4 because I had the same questions that Dr. Litman
5 did initially about we have fentanyl in a
6 transmucosal formulation and we don't even use that
7 in the hospital. But looking at that, that is only
8 indicated for patients that are opioid tolerant.
9 And if you look at the way the dosage form works in
10 the lollipop, it's something that's more for
11 chronic pain than -- it wouldn't be usable in the
12 current formulation in the acute setting that we're
13 talking about.

14 So I think there is still an unmet need for
15 something that is more rapidly available
16 sublingually than what we have on the market right
17 now.

18 DR. ZACHAROFF: Okay. One more thing we're
19 going to vote on before we actually vote, and that
20 is we were scheduled to have a break at 3:00 p.m.
21 and then come back and continue.

22 MALE VOICE: [Inaudible - off mic].

1 (Laughter.)

2 DR. ZACHAROFF: Okay. So the consensus is
3 to carry on and go to the vote. I'm assuming there
4 are no further questions or comments, and that
5 means that we will begin voting in a moment. Just
6 to let you know, we will be using an electronic
7 voting system for this meeting. Once we begin the
8 votes, the buttons will start flashing and will
9 continue to flash even after you have entered your
10 vote. Please press the button firmly that
11 corresponds to your vote. If you are unsure of
12 your or you wish to change your vote, you may press
13 the corresponding button until the voting is
14 closed.

15 After everyone has completed their vote, the
16 vote will be locked in. The vote will then be
17 displayed on the screen. The DFO will read the
18 vote from the screen into the record. Next, we
19 will go around the room and each individually state
20 how we voted and our name into the medical record.
21 And you may also opt to state the reason why you
22 voted as you did, if you'd like. We will continue

1 in the same manner until all questions have been
2 answered or discussed before we adjourn.

3 I'm going to read the question at hand.
4 Overall, do the benefits of sufentanil sublingual
5 tablets, 30 micrograms with the REMS proposed by
6 FDA outweigh the risks for the management of
7 moderate to severe acute pain, severe enough to
8 require an opioid analgesic and for which
9 alternative treatments are inadequate in adult
10 patients in a medically supervised setting,
11 supporting approval of sufentanil sublingual
12 tablets, 30 micrograms?

13 (Voting.)

14 DR. ZACHAROFF: Everyone has voted. The
15 vote is now complete.

16 DR. CHOI: For the record, we have 10, yes;
17 3, no; and zero abstentions.

18 DR. ZACHAROFF: So let's go around the room.
19 If we could start on this side of the table.

20 DR. MEISEL: Steve Meisel with Fairview. I
21 voted no for a number of reasons, many of the
22 reasons I've already stated. But I think in terms

1 of efficacy, I think the onset is too slow. That
2 will lead to dose stacking and repeated doses.

3 The population that's being described is too
4 broad. I can see this in an ED setting or
5 battlefield situation, but in any other
6 circumstance, the idea of not having an IV line, I
7 don't see that indication. I don't see the value
8 there. I see lots of risks in those settings.

9 No IV line means no IV naloxone, and I think
10 that's a serious risk. We don't know what the
11 equivalent doses are. I've never come across a
12 opioid drug for approval that I can't tell you what
13 the equivalency is in terms of morphine. The 30
14 milligrams equals 5 is highly inaccurate.

15 The issues of dose titration and flexibility
16 I think are problematic. It will end up being used
17 in ways that are unsafe and dangerous. The
18 experience of the elderly is nonexistent. We have
19 no idea how to dose it, if to dose it, and whether
20 to give it all in the elderly. I think that's
21 problematic.

22 A comment that probably doesn't really

1 relate to whether we should say yes or no or not,
2 but I think needs to get into the record is that
3 this product will create a tremendous amount of
4 plastic in the waste stream.

5 From an environmental point of view, I think
6 with all the plastic problems that we have in
7 oceans and every place else, the amount of plastic
8 for this product, for 1 dose of this product is
9 extraordinary. And I think that's to me is a
10 concern that doesn't lead to approval or
11 disapproval, but I think it's something that we
12 need to acknowledge.

13 MS. SHAW PHILLIPS: Marjorie Shaw Phillips.
14 I voted yes, but with some qualifications, and
15 that's really looking at some of the terms and
16 language. And I had a lot of the same concerns
17 that Dr. Meisel did, particularly for which
18 alternative treatments are inadequate. And then I
19 do see that benefit being in that narrow population
20 for somebody that you want to give something
21 immediately and your only other route is giving
22 intranasal something off label or a product that's

1 not often available.

2 So I think having a sublingual product for
3 that immediate use when there's no IV access is
4 certainly reasonable. I also agree with
5 Dr. Zacharoff about the term "medically supervised
6 supervised setting" needing to be further
7 delineated and stricter and have concerns about
8 dose stacking and time to effective pain relief.
9 But I think for at least a narrow indication, there
10 are some populations where this does have a
11 substantial risk-benefit profile because there
12 aren't suitable alternatives.

13 DR. FISCHER: Mike Fischer, Boston. I voted
14 no, and the reasons really focused more on the
15 efficacy. I echo a lot of sentiments of the two
16 panelists who already spoke. I was quite reassured
17 about the safety and the REMS and human factors and
18 so on. So for weighing risks versus benefits, that
19 by extension means I was pretty underwhelmed with
20 the efficacy, and that's especially in the
21 populations without alternatives.

22 As Dr. Meisel pointed out, the argument that

1 was made was that this is for patients who need
2 something very quick in these narrow windows where
3 it's hard to get IV or another option, and we saw a
4 relatively slow onset, which then to me begs the
5 question so what exactly is the niche where this
6 drug is most beneficial? And I didn't feel like I
7 had enough data to answer that question positively.

8 DR. LITMAN: Ron Litman. I voted yes for
9 the reasons I elaborated before. Just as a one
10 liner, I think that ultimately if this drug gets
11 approved, the ED physicians and the physicians in
12 battle will determine its usefulness. And I wasn't
13 concerned about the safety or public health.

14 DR. ZACHAROFF: This is Kevin Zacharoff. I
15 voted yes pretty much for reasons that have already
16 been stated.

17 DR. ZELTZER: Lonnie Zeltzer, and I voted
18 yes. I think there's certainly a need in a very
19 narrow population. And just a comment, if you give
20 an oral med because you can't -- I mean, a
21 swallowed oral med, not sublingual, because you
22 can't get an IV, and you're in this same issue with

1 giving an opioid reversal agent. So I don't think
2 that's unique to this. Anyway, I agree with the
3 reasons said.

4 DR. SHOBEEN: Abby Shoben. I voted yes. The
5 benefit I think is actually fairly comparable to a
6 lot of the other opioids that we've looked at and
7 that they establish it and many of the same ways
8 that we've seen it. That was pretty clearly
9 demonstrated for me. And the risks especially with
10 the REMS mitigating the risk of it being out in the
11 community make the risk both to the individual
12 patients and to the public health pretty minimal.

13 DR. KAYE: Alan Kaye, LSU. I voted yes. I
14 think there are benefits to a certain population,
15 and I think the risks certainly are satisfactory in
16 my view the way that the product will be intended
17 to be used.

18 DR. TERMAN: I'm Greg Terman from University
19 of Washington in Seattle. I voted yes because, in
20 my opinion, there was clear efficacy for acute pain
21 and minimal risks, at most, the same as other
22 opiates in the hospital. Also, it would fill a gap

1 in our current pharmacopeia for treating pain
2 quickly without an IV. I was not convinced so far.
3 I'm skeptical that that's actually going to be
4 true, that fast onset may or may not be true based
5 on the data, but that doesn't affect, for me, that
6 it is efficacious and safe.

7 MS. WILLACY: Jacqueline Willacy. I voted
8 no, and I admire a lot of your sentiment. I could
9 see it in an ER environment or on the battlefield.
10 In the acute care setting, I think it's going to be
11 very taxing on the nurses. For the stacking,
12 there's no titration process for this medication.
13 It's hourly, and it's going to require a lot of
14 monitoring.

15 A lot of patients, if you're not in the ICU
16 setting or a step-down setting, you don't have
17 continuous monitoring, so it's going to require
18 more. From a nursing perspective, it will require
19 nursing power, nursing hours, and just to keep
20 going back and forth to look at the patient to make
21 sure you're safe. I wouldn't recommend it for an
22 inpatient. Just about all our inpatients do have

1 an IV.

2 DR. WARHOLAK: Terri Warholak, and I voted
3 yes for reasons stated before that I will not
4 elaborate on. But while I have the microphone, I
5 wanted to commend the FDA for the good work that
6 you do. I don't think that many people in the
7 public know what you do or the lengths you go to do
8 it. And I've always been, every time I come here,
9 very impressed with the work that you've done. Not
10 only do you provide thoughtful reviews of the
11 sponsor's data, but you always do, or often do,
12 methodologically rigorous studies in-house as well,
13 and I don't think people know a lot about that, so
14 thank you.

15 DR. HIGGINS: Jennifer Higgins. I voted
16 yes, I guess maybe surprisingly to some people. I
17 was persuaded by the data in totality. What I
18 would suggest, though, is specific label language.
19 I would like to see something in there about
20 caution to be used with older adults with this
21 medication. I'd also like to see the sites -- just
22 like Dr. Zacharoff said, I'd like to see the site

1 spelled out. It could be something like where
2 intravenous opioid medications are already being
3 used or hospitals. I think it should be spelled
4 out, is what I think.

5 MR. O'BRIEN: Joe O'Brien, and I voted yes.
6 I wish I was voting yes to eliminate all opioids,
7 but it's a real world, and I think it behooves us
8 to do a better job at what we do. I think this is
9 one step to doing a better job for a very niche
10 patient population who has a need, so I support
11 that effort.

12 I also want to very much thank the FDA. It
13 is always a pleasure, and I think it was a great
14 job with what you did and what you always have to
15 do in terms of working with the sponsor to try to
16 work it out. And it's very evidenced by the
17 struggle we have around here to try to come to the
18 decisions that you have to come, and I thank you
19 for that.

20 DR. ZACHAROFF: I would like to say from the
21 FDA perspective that the presentations today from
22 the FDA I think really helped the committee a

1 tremendous amount to come to the conclusions and
2 create a lot of thoughts. So spectacular job on
3 the people who presented today.

4 Before we adjourn, I'd just like to ask if
5 there are any last comments from the FDA.
6 Dr. Hertz?

7 DR. HERTZ: Well, I would like to say how
8 much I appreciate the time and effort you all put
9 in. We keep dragging people across the country.
10 Thank you, Dr. Terman and others. And we know it's
11 no small thing to take time from what I appreciate
12 to be very, very busy lives. So thank you; always
13 helpful.

14 **Adjournment**

15 DR. ZACHAROFF: As we adjourn, panel
16 members, I just want to remind you to please take
17 all personal belongings with you as this room is
18 cleaned and emptied at the end of each meeting day.
19 Any materials left on the table will be disposed
20 of. Please also remember to drop off your name
21 badge at the registration table on your way out so
22 they may be recycled, and we will now adjourn this

1 meeting. Thank you.

2 (Whereupon, at 3:03 p.m., the meeting was
3 adjourned.)

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22