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

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Moon Hee V. Choi, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE MEMBERS (Voting)

Ronald S. Litman, DO, ML

Professor of Anesthesiology & Pediatrics

Perelman School of Medicine

University of Pennsylvania

Attending Anesthesiologist

The Children's Hospital of Philadelphia

Medical Director

Institute for Safe Medication Practices

Philadelphia, Pennsylvania

Abigail B. Shoben, PhD

Associate Professor, Division of Biostatistics

College of Public Health

The Ohio State University

Columbus, Ohio

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

(Acting Chairperson)

Faculty and Clinical Instructor

Pain and Medical Ethics

State University of New York, Stony Brook School of Medicine, Stony Brook, New York

Ethics Committee Chair

St. Catherine of Siena Medical Center

Smithtown, New York

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

TEMPORARY MEMBERS (Voting)

Michael Fischer, MD, MS
Associate Professor of Medicine
Harvard Medical School
Associate Professor of Epidemiology
Harvard T.H. Chan School of Public Health
Division of Pharmacoepidemiology &
Pharmacoeconomics
Brigham & Women's Hospital
Boston, Massachusetts

Jennifer Higgins, PhD
(Acting Consumer Representative)
Director of Research & Policy
Association of Developmental Disabilities Providers
Framingham, Massachusetts

Alan Kaye, MD, PhD
Professor, Program Director, and Chair
Department of Anesthesiology
Louisiana State University
New Orleans, Louisiana

Steven B. Meisel, PharmD, CPPS
System Director of Medication Safety
Fairview Health Services/Healtheast Care System
Minneapolis, Minnesota

Joseph P. O'Brien, MBA
(Patient Representative)
President & Chief Executive Officer
National Scoliosis Foundation
Stoughton, Massachusetts

Marjorie Shaw Phillips, MS, RPh, FASHP, CIP
Pharmacy Coordinator
Clinical Research and Education
AU Medical Center at Augusta University
Clinical Professor of Pharmacy Practice (without salary)
University of Georgia College of Pharmacy
Augusta, Georgia

Gregory Terman, MD, PhD

Professor

Department of Anesthesiology and Pain Medicine

and the Graduate Program in Neuroscience

University of Washington

Seattle, Washington

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

Professor and Assistant Dean

Academic Affairs and Assessment

College of Pharmacy

University of Arizona

Tucson, Arizona

Jacqueline A.M. Willacy, RN

Clinical Critical Care Nurse

Department of Veterans Affairs

Washington, District of Columbia

FDA PARTICIPANTS (Non-Voting)

Sharon Hertz, MD

Director

Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Office of Drug Evaluation II (ODE-II)

Office of New Drugs (OND)

CDER, FDA

Janet Maynard, MD, MHS

Clinical Team Leader

DAAAP, ODE-II, OND, CDER, FDA

Ning Hu, MD, MS

Medical Officer

DAAAP, ODE-II, OND, CDER, FDA

Cynthia LaCivita, PharmD

Director

Division of Risk Management

Office of Medication Error Prevention and

Risk Management (OMEPRM)

OSE, CDER, FDA

Irene Chan, PharmD, BCPS

Deputy Director

Division of Medication Error Prevention and

Analysis

OMEPRM, OSE, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

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

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

DR. HERTZ: Good morning. I am Sharon

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

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

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

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

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

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

MS. SHAW PHILLIPS: H. Marjorie Shaw

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

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

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

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

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

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

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

DR. SHOBEN: Hi. I'm Abby Shoben. I'm an associate professor of biostatistics at the Ohio State University.

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

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

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

DR. WARHOLAK: Good morning. I'm Terri

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

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

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

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

DR. ZACHAROFF: Thank you all.

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

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

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

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

Conflict of Interest Statement

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

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

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

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

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

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

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

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

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

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

Merck and Company.

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

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

FDA Opening Remarks - Sharon Hertz

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

severe acute pain in medically supervised settings.

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

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

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

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

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

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

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

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

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

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

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

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

DR. ZACHAROFF: Thank you.

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 advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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

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

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

We will now proceed with AcelRx Pharmaceuticals' presentations. Thank you.

Applicant Presentation - Pamela Palmer

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

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

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

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

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

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

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

Currently, transmucosal opioids for analgesia are only available for treatment of opioid-tolerant patients with cancer or for chronic pain. Avoiding the IV route of administration aligns with the latest guidelines on postoperative opioid pain management, which recommend oral over IV opioids. Importantly, the sublingual route also benefits patients with difficult IV access. However, few opioids have the appropriate physicochemical properties for effective sublingual

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We agree with the FDA that the results of

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

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

In addition to the REMS attestation, AcelRx

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

With this background in mind, let me review the agenda for the remainder of our presentation. Dr. Jim Miner will discuss the unmet need. Dr. Dennis Fisher will then present the clinical pharmacology that differentiates DSUVIA from other analgesic options. I will turn to present the efficacy results from our clinical program, and Dr. Neil Singla will follow with the safety results. I will then return to review our educational materials, REMS program, and conclude the presentation.

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

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

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

Applicant Presentation - James Miner

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

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

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

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

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

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

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

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

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

Lastly, there are many challenges to

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

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

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

Imagine a patient arriving at the hospital

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant Presentation - Dennis Fisher

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

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

The 30-microgram dose has been selected to

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

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

concentration.

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

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

Unfortunately, there's no IV dose of sufentanil that yields both an acceptable Cmax and an intermediate duration of action. I note that this is not unique to sufentanil. The same limitation applies to other lipophilic opioids such

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

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

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

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

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

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

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

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

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

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

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

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

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

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

only slow onset of analgesia, but also complicate titration.

If intravenous morphine is slow on onset, consider what happens when morphine is administered orally. Not surprisingly, absorption delays the pharmacokinetic profile and slows the onset of analgesia compared to IV administration. Therefore, the gastrointestinal route of absorption with oral opioid medications may not be optimal for patients requiring rapid relief from moderate to severe pain, and oral morphine is unlikely to result in a rapid onset of analgesia. In contrast, DSUVIA can offer timely pain relief while avoiding the IV route of administration.

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

Applicant Presentation - Pamela Palmer

DR. PALMER: Thank you, Dr. Fisher.

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

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

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

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

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

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

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

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

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

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

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

We also evaluated the onset of analgesia.

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

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

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

Patients mean age was in their early 40's.

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

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

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

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

Now, turning to the primary endpoint

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant Presentation - Neil Singla

DR. SINGLA: Thank you, Dr. Palmer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

least 24 hours.

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

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

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

provide further support to the safe use of sufentanil tablets.

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

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

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

for use.

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

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

The human factor study demonstrated that healthcare professionals can successfully

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

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

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

Applicant Presentation - Pamela Palmer

DR. PALMER: Thank you Dr. Singla.

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

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

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

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

In summary, DSUVIA's sublingual

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

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

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

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

Clarifying Questions

DR. ZACHAROFF: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. MEISEL: So you're suggesting that every

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PALMER: Yes.

DR. MEISEL: Okay. Thank you.

DR. ZACHAROFF: Dr. Higgins?

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

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

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

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

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

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

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

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

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

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

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

to make sure you monitor these patients.

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

DR. HIGGINS: Thank you.

DR. ZACHAROFF: Dr. Warholak?

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

DR. ZACHAROFF: Move to the mic closer.

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

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

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

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

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

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

DR. WARHOLAK: Yes. Thank you.

DR. KAYE: It's slide 54.

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

DR. WARHOLAK: Thank you. Then finally, on

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

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

DR. WARHOLAK: Yes.

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

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

DR. ZACHAROFF: Dr. Litman?

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

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

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

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

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

here.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Could you tell us theoretically how that would work?

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

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

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

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

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

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

dropped pills.

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

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

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

DR. LITMAN: Thanks very much.

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

DR. LITMAN: Got it. Thank you.

DR. ZACHAROFF: Mr. O'Brien?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PALMER: Dr. Miner?

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

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

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

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

DR. MINER: I don't.

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

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

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

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

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

clinician, what would I do?

DR. MINER: Work on starting an IV.

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

DR. MINER: Yes.

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

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

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

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

DR. ZACHAROFF: What medication was used for rescue?

DR. PALMER: This was IV morphine.

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

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

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

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

DR. ZACHAROFF: So in study 202 --

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PALMER: Yes.

DR. ZACHAROFF: Okay. Thank you.

Dr. Terman?

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

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

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

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

DR. TERMAN: Okay. Good. Thank you.

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

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

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

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

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

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

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

Could you talk about that?

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

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

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

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

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

DR. PALMER: Sure.

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

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

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

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

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

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

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

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

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

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

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

DR. PALMER: Yes.

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

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

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

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

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

decrease.

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

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

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

DR. PALMER: And just to clarify for the

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

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

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

are on baseline opioids?

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

DR. ZACHAROFF: Ms. Phillips?

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

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

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

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

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

Then moving forward beyond the initial

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

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

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

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

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

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

DR. KAYE: The use of naloxone.

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

DR. KAYE: Thank you very much.

DR. PALMER: Yes. Sorry for misunderstanding that.

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

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

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

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

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

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

different doses and achieve different concentration levels.

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

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

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

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

FDA Presentation - Ning Hu

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

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

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

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

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

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

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

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

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

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

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

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

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

selected safety data from the 15-microgram tablet program.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The applicant performed pooled safety

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

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

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

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

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

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

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

Second, the applicant predicted the clinical

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

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

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

depression.

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

FDA Presentation - Otto Townsend

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We determined that the data did not support

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

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

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

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

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

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

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

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

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

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

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

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

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

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

strategies, or REMS, for the product.

FDA Presentation - LaShaun Washington-Batts

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The FDA's proposed REMS goal is to mitigate

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

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

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

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

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

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

FDA Presentation - Ning Hu

DR. HU: I will end the presentation with

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

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

If sufentanil sublingual 30-microgram tablet

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

Clarifying Questions

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

Mr. O'Brien?

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

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

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

(Crosstalk.)

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

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

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

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

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

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

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

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

DR. WASHINGTON-BATTS: Yes, sir.

MR. O'BRIEN: That would?

DR. WASHINGTON-BATTS: Yes.

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

DR. ZACHAROFF: Dr. Higgins?

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

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

DR. ZACHAROFF: Dr. Zeltzer?

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

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

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

DR. ZACHAROFF: Dr. Terman?

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

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

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

DR. MAYNARD: This is Janet Maynard from

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

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

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

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

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

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

carry out the pain score for a few hours.

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

DR. TERMAN: Okay. So just one hour.

DR. REN: Yes.

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

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

we're really studying something that supports the indication.

That's all I have. Thanks.

DR. ZACHAROFF: Thank you. Dr. Litman?

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

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

anything here.

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

DR. LITMAN: Sure.

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

DR. LITMAN: Picking it up, sure.

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

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

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

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

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

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

So the goal was how do we keep this small

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

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

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

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

it?

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

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

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

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

DR. ZACHAROFF: Thank you. Ms. Phillips?

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

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

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

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

DR. ZACHAROFF: Thank you.

Mr. Thompson [sic]?

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

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

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

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

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

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

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

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

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

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

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

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

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

Dr. Fischer?

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

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

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

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

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

DR. ZACHAROFF: Dr. Shoben?

DR. SHOBEN: I also have questions about the

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

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

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

clinical experience.

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

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

DR. ZACHAROFF: Dr. Terman?

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

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

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

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

DR. TERMAN: Sure.

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

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

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

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

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

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

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

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

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

DR. ZACHAROFF: Dr. Palmer?

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

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

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

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

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

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

DR. ZACHAROFF: Thank you. Dr. Zeltzer?

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

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

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

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

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

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

DR. ZELTZER: Thank you.

DR. ZACHAROFF: Dr. Meisel?

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

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

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

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

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

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

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

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

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

DR. HERTZ: No. And -- no.

MR. O'BRIEN: No.

(Laughter.)

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

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

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

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

DR. HERTZ: Sure. Dr. Zacharoff?

DR. ZACHAROFF: Sure.

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

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

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

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

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

DR. PALMER: Yes.

MR. O'BRIEN: Okay. Thank you.

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

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

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

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

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

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

(No response.)

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

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

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.

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

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

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

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

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

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

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

When I first learned about DSUVIA, I was

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

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

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

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

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

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

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

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

afternoon.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

dosed patients under anesthesia with this drug.

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

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

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

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

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

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

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

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

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

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

purposes of the record.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(No response.)

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

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

DR. HUTCHINS: Good afternoon. My name is

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

I'm here today to discuss acute pain control and the role that DSUVIA can play in treating our patients that are in institutions across the United States. Acute pain control remains one of the most important, if not the top concern, of patients coming into surgery today, and multiple surveys from the 1990s, 2000s, and 2000 teens have shown that a good portion, the majority of patients, still have moderate to severe pain after surgery.

Poor pain control can lead to many negative effects on patients, not limited to impacts on immune function, hypercoagulability, and decreased GI motility. Furthermore, uncontrolled acute pain

can lead to persistent pains issues after surgery and even impacts the overall healthcare systems as it can contribute to delays in PACU stays, delays in discharged from the hospital, and readmissions for pain.

The optimal approach to acute pain management as a multimodal approach involves two or more different types of pain medications to treat this. For those surgeries or injuries in which acute pain is mild or mild to moderate, this can usually be treated with non-opioid medications such as acetaminophen, nonsteroidal anti-inflammatory drugs, or local anesthetics.

However, when patients experience moderate or moderate to severe pain, opioids are typically needed in conjunction with the aforementioned medications. This has been shown with both the American Society of Regional Anesthesia and the American Society of Anesthesiologists, both of which I'm a member of, that I've recommended in these moderate and moderate to severe patients that opioids we need to treat these patients.

I do believe this is an unmet need, and we see this with the advent and the more progression of enhanced recovery after surgery programs and institutions across United States. There's a push for the move away from intravenous opioids in these patients that are having moderate to severe pain to improve their recovery and get them moving and participated in therapies and out of the hospital sooner.

What happens now is we move from an IV to an oral opioid, with the oral opioids having a slower onset of action. And because they're in this moderate to severe pain, we've seen an escalation in the dose of the oral opioids. So we've oxycodone or Vicodin dosages from the 5 to 10 typically being moved up to 15 to 20. And unfortunately, as providers are less comfortable with these medications, as they get through their stay, if they stay on these doses of 15 to 20 of oxycodone or higher doses of hydrocodone, they're discharged on these higher dosages.

This medication can be used as a bridge

either from the operating room until they're able to go onto their oral medications that they can then take home or as a bridge from the IV to the sublingual, and then to the oral as they're able to go home. As they've talked about earlier today, people do not go home on this medication.

DSUVIA is a medication that's able to be easily administered. It's sublingually given. It really is designed to minimize diversion, and we've seen this with the ability to avoid intravenous medications, as they're more easily able to divert in this type of a medication. It's rapidly reduced patients moderate to severe pain in the clinical trials and showed that these patients tolerated this medication quite well, even though the elderly patients tolerated it well and those with impaired renal function.

Additionally, the safety profile and adverse events seen in these clinical trials was consistent with what we've seen in other opioids. So this is not providing any new adverse events that we haven't seen in other opioid medications. These

results illustrate DSUVIA not only effective in reducing pain but safe in a way that has minimal adverse effects.

In conclusion, I believe that DSUVIA is a medication that could provide effective pain relief but also with minimal adverse events as long as a risk evaluation and mitigation strategy is employed and patients are kept in a medically supervised setting. Thank you very much.

DR. ZACHAROFF: Thank you. Will speaker number 9 please step up to the podium, introduce yourself, and for the record, please state your name and any organization you are representing.

DR. WEBSTER: Hello again. I'm Lynn Webster, vice president of scientific affairs for PRA Health Sciences. I'm speaking only for myself and have not been compensated for my time or expenses. Also, I've not been involved in any phase of DSUVIA's development.

There are two questions I would ask the committee to consider today. First, is there a need for an opioid with the characteristics of

DSUVIA? And second, is the safety profile of DSUVIA acceptable? Regarding the need, everyone recognizes there is a serious opioid crisis in the United States. Many measures have been taken to address the problem. Some efforts have resulted in fewer opioids being prescribed. This is not necessarily bad, but it has had or led to unintended consequences.

Inadequately controlled acute pain can increase the risk of chronic pain. Many academic publications have reported that undertreated pain increases the risk of dementia, memory loss, and premature mortality. As an advocate for people in pain, I want to see the most suffering among us receive the compassionate care they deserve.

Because of the risks associated with prescribing opioids, many physicians are choosing not to treat their patients who have severe pain. Even hospitals, pain is frequently undertreated. A recent New England Journal of Medicine Commentary by Dr. Eduardo Bruera from MD Anderson states that in his institution, there's been serious shortages

of parenteral opioids necessary to provide relief from cancer-related pain.

Unfortunately, his cancer center is not an exception. There's a national shortage of parenteral opioids. We heard this yesterday at this meeting, particularly in cancer centers as a direct result of government interventions to curb the opioid crisis. Providers are now often forced to find alternative means to meet the needs of their patients, and frequently, the options are inadequate.

Parenteral opioids are desirable due to the immediate and reliable analgesia. Many patients requiring postoperative an palliative pain relief are not able to take oral analgesics. DSUVIA is a rapid onset, sublingual analgesic that is similar to parenteral opioids in onset and avoids oral ingestion. Therefore, DSUVIA could help fill an unmet need.

The second consideration is regarding safety. I'm quite familiar with sufentanil having used it extensively in the operating room and in

labor and delivery for years as a practicing anesthesiologist. I also used it off label with intrathecal delivery systems for chronic pain. It's a potent opioid that can provide clinical benefits to the appropriate patients.

DSUVIA has inherent risks that are typical of other opioids, including addiction and overdose deaths. However, the context in which an opioid is used in managed may be more important than the inherent pharmacologic risks of a product.

In other words, we should ask the following questions. For whom is the drug intended, and is there a risk mitigation strategy to ensure the drug is used properly? Who should be authorized to prescribe the product? How would the prescribers and those dispensing the drug be trained to ensure the safest possible use? How can a patient be prevented from taking more than intended?

Since diversion from well supervised hospital settings is very uncommon for all opioids, we can trust there will probably be systems in place to mitigate diversion. So the major concern

with the product would be inappropriate use. This morning, AcelRx stated that provider education is a key component to their risk mitigation strategy to ensure appropriate use.

Therefore, it would appear that with a robust provider education program proposed by AcelRx, DSUVIA could help fill an unmet need by the shortage of parenteral opioids with minimal risk of harm to patients and to society. Thank you for your attention.

DR. ZACHAROFF: Thank you. Will speaker number 10 please step up to the podium, introduce yourself, and please state your name and any organization you are representing for the record.

DR. SRINIVASAN: Hi. Thank you for your opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a masters of public health from Johns Hopkins University. I'm a senior fellow at the National Center for Health Research, which analyzes scientific and medical data to provide objective health information to patients, health professionals, and policy makers.

We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

We have strong concerns about the safety of the drug in question today, sufentanil. First, we are concerned that the level of pain relief provided by sufentanil is not clinically meaningful. Patients taking the drug had statistically lower levels of pain than patients taking placebo based on their SPID scores, but this difference was so small, I would not consider it helpful to my patients.

Just as important, there was no statistical significant difference in how long it took for patients to expedience meaningful pain relief between placebo and this drug that is supposedly 5 times more potent than fentanyl. If it really were more effective than placebo, surely it would work more quickly to relieve pain than the placebo.

The weak results are even more problematic because there was only one pivotal phase 3 clinical trial. We have an opioid epidemic, and it's

crucial that the FDA not approve opioids that are not proven to work.

There is also limited diversity in the clinical trials in terms of age, race, and clinical conditions. Most of the study patients are white, and many were under the age of 50. We would assume that a wide variety of patients visit the ER or undergo surgery, but that diversity is not reflected in the study population. The sponsor also failed to look older patients in trials of sufentanil 30 microgram and extrapolated the data from 15 microgram even though we know that pain tends to increase with these.

In summary, this drug has not proven to have a meaningful effect or impact on reducing pain in postoperative settings. I respectfully urge you to let the FDA know that the agency should require better evidence of the efficacy of this drug. The sponsor should submit more conclusive data to this advisory committee before it can consider recommending approval for sufentanil. Thank you.

DR. ZACHAROFF: Thank you. Just checking to

see if speaker 7 has arrived.

(No response.)

DR. ZACHAROFF: It doesn't appear so.

Okay. Then we have reached the conclusion of the open public hearing session. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments made. We will ask Dr. Hertz to provide us with the charge to the committee.

Charge to the Committee - Sharon Hertz

DR. HERTZ: Thank you. This is Sharon Hertz. Once again, you've heard a lot of information this morning. You've heard about the safety and efficacy data for DSUVIA, sufentanil sublingual tablets in a 30-microgram dose for management of moderate to severe acute pain, severe enough to require an opioid analgesic for which alternative treatments are inadequate in adult

patients in a medically supervised setting.

You've heard about some of the differences of opinion between the agency and the sponsor. I think onset of action was one of the big ones. You've heard about the risk mitigation strategy that's been proposed.

Now we're going to ask you to discuss each of those things and tell us what you think about the available efficacy data, safety data, and whether you think the information from human factors studies in the clinical trials inform how to use the product safely and effectively, and also whether the REMS can achieve what it's intended to, which is to prevent the product from going home. That's really the focus more than children in the hospital. It's really more outside. I think we got a little sidetracked.

We also want to hear if you think that this product -- it would be the first sufentanil product not used in the context of the OR, so what impact that may have for some of the problems with abuse and misuse. Then based on all of these points,

please let us know if you think this product should be marketed, and as important as the vote is why you've made your decision to support that vote.

Thank you for your time and consideration, and back to you, Dr. Zacharoff.

Questions to the Committee and Discussion

DR. ZACHAROFF: Thank you, Dr. Hertz.

Just before we get to the questions, I would like to urge the panel members that while we do encourage discussion about the topics, we don't want you to tell us what your vote is. We'll leave that for the actual vote itself. So we're very interested in engaging in discussion of the questions as they arise.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Question 1 for discussion, discuss whether the data are adequate to support a finding of

efficacy for sufentanil sublingual tablets 30 micrograms for the proposed indication, the management of moderate to severe acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adult patients in a medically supervised setting.

If there are no questions or comments concerning the wording of the question, we will now open the question to discussion by the panel. Dr. Meisel?

DR. MEISEL: Steve Meisel with Fairview in Minneapolis. I was really intrigued by this product, but I think I'm disappointed with the data because I don't think we have data to answer this question. There are no comparative efficacy studies with any other narcotic or non-narcotic medication. We have no idea whether this drug works as well as, or better than, or worse than ibuprofen, acetaminophen, aspirin, or morphine. We have placebo-controlled trials, but that's about it.

The onset of action, the maximum onset of

action or the peak action is in an hour. That's pretty slow for a drug that's supposed to be used for really acute pain. There are some safety concerns that go along with that we'll talk about on the next question or two. But, boy, for a situation where you have surgery and you're expecting moderate to severe pain, and you've got a drug that we have no idea whether or not it's as good as, better than, or worse than any other narcotic on the market because there's no data, that concerns me.

I think the answer to this question is no. I don't think the data are there to support or refute. I mean, maybe it does. Maybe it is effective, but the data presented today doesn't address that one way or another.

DR. ZACHAROFF: Thank you. And just a reminder, as we enter discussion, please identify yourselves before your statement.

Dr. Fischer?

DR. FISCHER: Mike Fischer, Boston. I'll be brief echoing on Steve's point. Looking at the

discussion question, there are two elements that we're dealing with here. One is, is it severe enough to require an opioid analgesic? And as was pointed out, we certainly are dealing with situations where there's pain that is severe enough to be treated, but is it at a level where that opioid analgesic's required?

It's hard to say. Certainly, it's clearly better than placebo, but it's the alternative treatments that are inadequate that really bugs me. But we heard some really compelling anecdotal descriptions of clinical scenarios. The ER patient who is elderly, a burn patient; there are situations where immediate IV access can be very difficult. That's compelling anecdotally, and we all can think of -- clinicians can think of cases like that. But I didn't have a sense that that is most frequent, and those weren't really the kinds of patients about whom we saw data. We saw data about the kinds of patients in who it's relatively easy to get IV access.

So I feel like that alternative treatments

are an inadequate point. I have reservations about whether that has been addressed adequately in the data that we've been shown today.

DR. ZACHAROFF: Thank you. Dr. Litman?

DR. LITMAN: Thank you. Ron Litman, Children's Hospital, Philadelphia and ISMP. I apologize for not doing this earlier in relation to these other questions. The FDA showed slide 16, and I'm wondering if either the FDA or the sponsor could give us more granular details about this time to onset, time to meaningful pain relief, SAP 301.

DR. HERTZ: This is Sharon Hertz. We have a very standard approach for determining the time to onset, and that is we think the best approach is to actually ask the patient to let us know when they feel onset. Patients usually can't detect a statistically significant difference in pain curves, but they can tell us when they start to feel an effect. So that would be the actual clinical onset.

We do 2 stopwatches because the first one can sometimes be pretty variable surprisingly not

as much with NSAIDS, but certainly with opioids. And they're not quite sure. Maybe it's starting. So that's why we start off with first perceptible, but then what we really want to know is when they're starting to get some real pain relief. So that's why there's a second stopwatch.

DR. LITMAN: And the meaningful is the second stopwatch.

DR. HERTZ: Yes. And that's the standard that has been used for decades. As you all know, we've been challenged to understand how to evaluate pain and pain relief beyond actually asking patients because people want some type of objective measure. But pain is subjective, and meaningful pain relief, the onset of pain relief is a subjective concept that only the patient can answer for themselves.

So that's why we use the double stopwatch method, and that's why we select the time for meaningful pain relief, the median time for meaningful pain relief. And what that means is there are going to be people for whom pain relief

is earlier and people for whom it's later. We choose the median as the best estimate on this.

DR. LITMAN: For this drug, are those curves available? I want to get a better idea. I'm looking at -- the median to me, with a 95 percent confidence intervals, is 42 to 72, which to me is kind of like the same as an oral oxycodone, approximately. But the range is really strange. It's 4 minutes to 4 hours.

DR. HERTZ: Some people did not register an onset. I suspect that kind of a number is some type of error.

DR. LITMAN: No, of course. But I'm just curious if there were curves associated with these tables, so we can get a better graphical --

DR. HERTZ: We don't usually look at curves for onset.

DR. LITMAN: Not onset but --

DR. HERTZ: I don't think we have --

DR LITMAN: I just think it would give us a nice idea of the population distribution and what their meaningful pain relief values were, if it's

available.

DR. HERTZ: I don't think we have it prepared as a slide, so sorry about that.

DR. LITMAN: Okay. Thank you.

DR. ZACHAROFF: Thank you. Dr. Terman?

DR. TERMAN: Greg Terman from University of Washington, Seattle. I do think that there's data to support efficacy for pain in the data, particularly if you combine the various studies, including open label. I think the open-label curves might give a bit of an indication that people do seem to get better in terms of their pain. It's not specifically the question you were asking, but it does appear that people's pain can improve.

The question is really does it fit in the landscape for what we're lacking. As was mentioned in the public comment period, we really are lacking a nice sublingual to send home with people that can't swallow so they don't have to be on IV medications, something that for whatever reason, their gut's really not working. And trying to find

a way to help those people would be really good. And because of the REMS situation, in particular this REMS, that won't happen with approval of this drug. It will not be going home with people who can't swallow.

The other hole in the landscape is something fast acting, as I mentioned earlier, and that really would be great. But what I'm seeing is that people kind of get better after a couple of hours. And in the IV comparison that was referenced by the sponsor, IV morphine comparison with the PCA sublingual sufentanil that was published, even then, there's really no difference for a couple of hours.

You look at the onset time, it wouldn't be bad if it was similar to morphine onset. It's a little less enthralling if it's similar to the oxycodone, so that in an emergency situation where you don't have an IV, maybe just give them oxycodone. So I do think it's efficacious. I'm just not sure it fills a niche, but I'm not telling you my vote.

DR. ZACHAROFF: Thank you. I think I may be the only one -- Mr. O'Brien, did you have something you wanted to say?

MR. O'BRIEN: Yes. Again, it's always depending on what the question is here. We found from previous meetings, yesterday and whatever, to say, okay, from a regulatory standpoint, you have this standard where you have to show that in fact the drug that's being put before is better than a placebo. Well, the FDA tells me that in fact the data is adequate to show that it is better than a placebo. So from that perspective, I would say yes.

The rest of the question says for which there are no better alternative treatments, are inadequate. I would agree with Dr. Meisel that as I went through this, I kept on questioning the population. I don't know if these patients really needed what they got. It was not that clear to me as I went through it that these patients really need it. I don't know, but that wasn't a question that I was asked.

I heard during the patient population that there are in fact comparative drugs that may be available with similar sublingual drugs, and may not have the same delivery system, but sublingual. I don't know that. I'm not a professional in that area. I'm not a pharmacist or an anesthesiologist, so I think that would be very important to know whether or not -- because we weren't asked about superiority to a comparator drug. We were just asked does the data show that it supports.

So I'm told the data supports. I'm not quite sure it's needed. I think there are clearly needs. As I expressed anecdotally, I can definitely see -- personally speaking, when I was in that ambulance, if I could have got that sublingual drug, I would have greatly appreciated it. It was needed. They couldn't get an IV in. And you didn't have to worry about what my indication was because I was balled up in agony and pain, grunting like an animal. And when I stopped grunting like an animal, you knew it was working, in that particular case.

Again, it depends on what the FDA is asking the question for. I accept that they tell us that the data shows that it is better than the placebo, but I have questions about that.

DR. HERTZ: This is Sharon Hertz. Can I just clarify? Our standard is not better than placebo for efficacy. Our standard for an analgesic efficacy study is to show that there is efficacy that is superior to some comparator. And the reason for that is if you simply look to see in an analgesic study, without what we call downside sensitivity -- if you just look to see if something is the same as a comparator, we don't know if that means both work or both don't work.

So what we would consider ideal would be to have a placebo and an active comparator, and we often discuss this with companies. So we may not be in a position to impose a requirement of an active comparator, but there's no reason why a sponsor cannot include that in one or several studies to determine how the product is performing relative to other things.

MR. O'BRIEN: Thank you very much for that clarification. In that case, I think it would be very important and very useful for the sponsor to take that next step and show that, in fact, it is better than a comparator because they have a great delivery system that I'm very much in favor of, but I think the other questions have to be answered as well.

DR. ZACHAROFF: Dr. Zeltzer?

DR. ZELTZER: Lonnie Zeltzer, UCLA, Los Angeles. First, I think your comment, Mr. O'Brien, without a comparator -- I mean, we know that it seems better than placebo. We don't know if it's better than what else is out there for acute, moderate to severe pain. I guess the very narrow area in which I don't think we have other agents is in the acute setting of the emergency department or in another acute setting where an oral agent cannot be tolerated for various reasons and while attempting to get an IV in, especially if it's difficult to get an IV in an individual.

So one has a very smaller area where I do

see a need that we don't have right now, which is a smaller window than what is being asked for here.

As was mentioned, it would be nice to see a comparative study of morphine, or dilaudid, or some other agent, oxycodone, acetaminophen. But for those who cannot tolerate an oral agent or while waiting for an IV, I don't know another comparative that we have at this point.

DR. ZACHAROFF: Thank you. Dr. Kaye?

DR. KAYE: Alan Kaye, LSU. I think it's efficacious, and I think there is a niche beyond placebo for the delays in oral onset. And I think that there is a niche for IV for the reasons a number of people have mentioned, which is you can't always get an IV and it can be problematic and delayed.

So I think the way I read this question is that, yes, it's efficacious and that it serves a purpose where alternative treatments are inadequate in adult patients in a medically supervised setting.

DR. ZACHAROFF: Just lastly, before I

summarize, my only point of discussion for this question is the last three words in the question, and that's "medically supervised setting." We had some discussion earlier in the day about what the definition was. We heard some thoughts from the sponsors about a willingness to possibly narrow in the scope of that.

For me, I think there probably has been enough data presented to support efficacy in a hospital setting. Medically supervised setting means so many different things to me that I could imagine we could end up in surgicenters, and walk-in clinics, and anyplace else. If I'm thinking about this medication as one that might potentially be administered to a patient, readministered to a patient over some period of time, a medically supervised setting just doesn't cut it for me.

So I haven't been satisfied in the scope of the definition as presented that the data was adequate because it doesn't say hospital setting.

DR. PALMER: Could I address the fact that

we have active comparator data?

DR. HERTZ: You can't start presenting new data now. You did not submit active, well-controlled, with downside sensitivity data for us to review here.

DR. PALMER: It's Zalviso active comparator data that's on file for Zalviso with the NDA.

DR. HERTZ: What would you like us to do with that now?

DR. PALMER: I just have one slide.

DR. HERTZ: Sure.

DR. PALMER: Thank you. So just to clarify, our first product was Zalviso, and we actually did a head-to-head comparator against IV morphine. I'll just quickly cover this. I'm talking about pain intensity difference, so that means a positive number means better. The pain intensity difference from placebo was greater as it goes up.

You can see here that Zalviso from a sublingual is 177 patients. Sublingual sufentanil had a more rapid pain intensity difference from baseline than morphine. It eventually caught up;

morphine caught up at about hour 6. And this is because it's not as lipophilic as sufentanil is. After we already knew we were faster than IV morphine, when we did the DSUVIA studies, we did not bother with a comparator because we had already demonstrated this, so I apologize.

DR. HERTZ: Dr. Palmer, this study I belief also had quite a bit of rescue in the Zalviso arm, and we're trying to confirm. Was this a blinded study?

DR. PALMER: No. This is open label, and there was very little rescue. There was only 2 milligrams in 48 hours.

DR. HERTZ: And what was the patient population? See, we don't have the information right now to adequately understand the conditions. We don't know the number of Zalviso doses. We don't know if the ultimate amount that accumulated over time was comparable to what's possible with DSUVIA based on the current dosing paradigm. We know that the accumulation in Zalviso was potentially much higher than the accumulation in

DSUVIA.

So let me thank you for presenting this, but I don't want it to go without saying that we don't have details for this study, the patient population, timing of the study. I mean, there's just a lot of information that isn't conveyed in a single slide.

DR. PALMER: This is in our briefing book. Sorry. This is not new data. This is in our briefing book for this NDA. We submitted this data. We also submitted oxygen saturation data showing that sublingual sufentanil has fewer patients with oxygen saturation below 95 than IV morphine.

DR. HERTZ: That was with Zalviso, correct?

DR. PALMER: Yes.

DR. HERTZ: In a different setting, different patient population.

DR. PALMER: Correct.

DR. HERTZ: Okay.

MR. O'BRIEN: I just want to make sure it is in your briefing book. I just want to be clear.

DR. ZACHAROFF: Thank you. And just as a reminder, no disrespect intended, but we're going to try to avoid that scenario if we can.

We do have one more comment for discussion, and that is Dr. Shoben.

DR. SHOBEN: Abby Shoben. Before all that, I'll just go ahead and comment and say that efficacy for me was clearly demonstrated. I agree with Dr. Kaye's point. And I don't actually think that we need an active comparator here in part because it's such a novel sort of delivery mechanism, and it's a potentially different patient population, proving that it's superior to placebo, which I think the data clearly show. It was enough for me.

Unlike situations where you have similar delivery mechanisms and it's a more obvious comparator, it was not needed in this setting for me, and it should be up to the physicians to figure out which ones they wanted to use for the patients in the future.

DR. ZACHAROFF: Thank you. Just to

summarize perspectives on the panel with respect to efficacy, some of us felt that the data may not necessarily be sufficient for us. Others felt that the novel delivery method, as we just heard, may not necessarily preclude the need for a comparison.

Some panel members felt that there might be an issue with respect to onset of action compared to other modalities that are out there, but this could very much be possibly compelling in patients were IV access is an issue.

We did hear from people that IV access doesn't necessarily mean that there's inadequate alternative treatments, but nonetheless, we did hear that in patients where there is a situation where IV access may not be obtainable, or people may not be able to tolerate oral medications, this medication could potentially be of value based on the data presented. We did hear feelings that a sublingual solution to opioid analgesia does meet an unmet need. And as we heard me state, a medically supervised setting is something that's unclear.

If there's anything I didn't capture, please let me know now.

(No response.)

DR. ZACHAROFF: Okay. If there are no further questions, we will -- Dr. Meisel?

DR. MEISEL: Steven Meisel from Fairview. Just one additional efficacy comment, and that is this is a fixed dose. U The 85-year-old grandma and the 350-pound linebacker are probably going to need different doses. The sponsor says, well, in those cases, yes, that's why we allow the dose to be given every hour. But that then is going to further delay the efficacy for people who need larger doses.

To me, that's an additional concern. I can't give 60 micrograms right away; I have to give 30 and wait an hour for the person who needs more. To me, I understand why it's a fixed dose. I understand the rationale behind that. But to me there's a safety concern with that, but there's also an efficacy concern, and that is the people who need higher doses have to wait an hour and let

it accumulate and maybe even get a third dose at hour 3 and let that accumulate. That to me is a significant efficacy concern.

DR. ZACHAROFF: Thank you for that addition, and that probably goes in line with what I mentioned earlier on in the day about lack of ability to titrate.

We will move on to question 2. Based on the available safety data, discuss any concerns that you may have about the safety profile of sufentanil sublingual tablets, 30 micrograms. If there are no questions or comments concerning the word of this question, we will now open the question to discussion.

Dr. Higgins?

DR. HIGGINS: I see no observed relationship between increased doses of the drug and AEs, however, I do still remain concerned about older adults and their decreased clearance with age and several other factors that make them a very vulnerable population that I feel hasn't been adequately studied to my satisfaction and do want

to say that I think they need extra care, and protection, and attention. And I would hope that this could be conveyed in some way, perhaps through labeling, if and when we approve the drug.

DR. ZACHAROFF: Thank you. Dr. Meisel?

DR. MEISEL: I agree with Dr. Higgins' comments about the elderly. In fact, the data are so weak in the elderly that if this drug were approved, I would think it would have to be limited to people under the age of 65 because there just isn't any data whatsoever in that space and the risks there are pretty high.

A couple of other points. A lot has been made about the fact that you don't have to have an IV line for this drug because it's sublingual. Well, no IV line also means that if you need to give rescue naloxone, you have no IV line. Now, there are other ways of giving naloxone, but it doesn't work as fast or as well as, as it does IV.

So you sort of take the good with the bad with this. And if somebody needs to be rescued and there is no IV line, that's going to be a serious

problem. That's a concern that I've got with this drug in the way that it's being proposed to be used, and I think we need to be cognizant of that.

The other point about safety here, as I mentioned before, because the 30 mgs may not be effective, the instructions for use will say wait an hour, but the real world will say that somebody is going to give rescue or something before that, at 15 minutes, at 30 minutes, or something, or they'll give another dose of this despite the fact that you're supposed to wait an hour.

The real world is the real world. That's what's going to happen. And we're going to end up with multiple narcotics on board, lots of dose stacking. That will happen with that, and I don't think that's been well elucidated and well characterized, but I think it's a reality that we need to recognize that is unique for this because of its delivery system and because of the fixed dose and the 1-hour dosing interval. So those are the additional safety concerns that I've got.

DR. ZACHAROFF: Thank you. Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. I agree with most of what's been said about the risks, and just from the totality of the data presented, I don't think that there's much of a risk, but mainly because I don't think it's just that potent of a drug. I think it's probably about the same as taking an oral oxycodone, although obviously without the oral has disadvantages if you can't swallow or if you've recently eaten.

That's one point. The other one, maybe I should have said this in the efficacy section. We've been talking a lot about anesthesia and post-op. I really don't see a role for this drug in the anesthesia peri-operative environment. I really can't think of a situation where an anesthesiologist would need this.

Honestly, there are very few adults, if any, that don't have an ivy coming out of surgery, a pre-op. I mean if you don't have an IV coming out of surgery. Pre-op, if you don't have an IV, that means you've come from home. I don't know, but you'd have to speculate on some unique painful

condition.

So it's really not a peri-operative drug. It would be very useful for the other scenarios we talked about like emergency room or in the military, but as far as safety goes, I haven't seen really much to make me very concerned. And although I agree, Dr. Higgins, about the elderly, I am comforted knowing that we give a lot more powerful drugs to the elderly through their IV in these same situations. So I don't think it's any more dangerous than that at all.

DR. ZACHAROFF: Ms. Willacy?

MS. WILLACY: Jacqueline Willacy. From a nursing perspective, we talk about stacking those every hour. It's very taxing on a nurse. You have 4 patients in ER or maybe on another unit where you have several patients, and if you have to go to give this medication on an hourly basis, it's not going to be effective because it's just a time timeframe where you're taking care of other patients. This is almost like it's a one-to-one patient because you're going back to the Omnicell

to get this medication to deliver this medication.

DR. ZACHAROFF: Thank you. Any other comments with respect to the available safety data and concerns we might have?

(No response.)

DR. ZACHAROFF: Okay. To summarize what I heard and make sure I captured it adequately, there was a sense that it's possible there might be insufficient data in patients over the age of 65 with respect to the data that was presented today. We heard that poor IV access might be a problem, especially if naloxone is necessary, which is conceivable that it will occur.

I was always taught that as an anesthesiologist, when you give a drug, you need to know how to take it back. I did have some concern from the safety perspective about a patient with a long bone fracture being given a sublingual medication and then being sent off to x-ray with no intravenous in and no ability to give an antagonist if it was needed.

When I think of people who are on opioid

therapy, I usually think of a 3 cc syringe, a needle, and an ampoule of Narcan nearby. So the fact of the matter is that if this is truly a bridge, as we heard some people mention in the open public hearing, then at best it's a bridge to being able to get an IV in after you've got pain controlled, not give pain control and then never have to put an IV in. So that was a safety concern of mine, which I agreed with Dr. Meisel.

Definitely we heard from a few people about the real-world issue of dose stacking and not knowing what people will do with patients who still have pain, because we do know that institutions get rated based on how satisfied patients were with respect to their pain management, and that ends up being a financial penalty if they don't get good HCAHPS survey scores. So in all likelihood, there is a concern, and we didn't necessarily see data about what will happen if patients are given medications, if this drug is ineffective.

Then lastly, and I'm very glad we heard this, about what the practicality might be of the

logistics of giving this medication on an hourly basis for a nurse, not only thinking about having to go to a patient's room to readminister this every hour, but also noting when it was actually administered, if the nurse is moving from patient to patient to patient, it might not actually get charted that it was given until some period of time after it was given, and that could throw off how well the pain is managed.

Did I leave anything out?

(No response.)

DR. ZACHAROFF: Okay. Good. Thank you.

So we will move on to the next question, question 3. Discuss whether data from the human factors studies and the clinical trials support the safe and effective use of the proposed product administered by healthcare professionals in certified settings such as hospitals, emergency departments, and surgical centers. In your discussion, consider whether the REMS proposed by FDA can be expected to mitigate the risks associated with dropped sufentanil tablets and

including the risk of accidental exposure.

Please take a minute to look at that lengthy question because I'm going to ask you if there are any questions or comments concerning --

MALE VOICE: Is that proposed by FDA [inaudible - off mic].

DR. ZACHAROFF: According to the wording of this question, it's REMS whims proposed by FDA.

Any other questions or comments concerning the wording of this question before we move to discussion?

(No response.)

DR. ZACHAROFF: Okay. Then we will now move to open the question to discussion. Dr. Warholak?

DR. WARHOLAK: Terri Warholak from University of Arizona. I really liked the REMS suggestions that the FDA made. and I feel like there were really good changes made to the instructions and to the plan. One of the things that I thought would be helpful for the future, especially since this involves the device, it might be really nice to give a placebo package to each of

the committee members so that we could play with it.

One of the things that I've found doing human factors training is everything seems simple until you do it. For example, even situations -- like I have a friend who bought a new refrigerator, and they were reading reviews online, and one of the reviews said that the ice cubes were hard to catch in your cup. And I thought, "Who can't catch an ice cube in a cup?" But it was so interesting because when you put the cup under the ice cube dispenser, it shot out and not down.

So it would've been really nice to just play around with one of the placebos before we came here so that we can have an idea of exactly how big it is and what some of the issues might be.

DR. ZACHAROFF: Thank you. Ms. Phillips?

MS. SHAW PHILLIPS: I also support the suggested changes to the REMS program that the FDA is recommending, particularly broadening the reach of the education to all personnel that really need to get it. I think in the grand scheme of things,

the issue with dropped tablets not being detected, particularly since the patient can sense the tablet or taste the tablet, in 80 percent of the cases is not as big an issue. And as was discussed with the meticulousness in the healthcare setting, it's much less likely for a dropped tablet to go unnoticed and get accidentally consumed.

I think the greater concern is the benefit-risk assessment, the targeted group of patients that really would benefit more from this, looking at the efficacy in the context of the REMS program that's needed, and also just being another fun drug of abuse that we would need to protect for getting outside of hospitals.

DR. ZACHAROFF: Thank you. Dr. Litman?

DR. LITMAN: Thanks. Ron Litman. I don't have a lot of concerns about the human factors. I don't have a great deal of confidence that the REMS, at least in this, will make a difference. However, the stuff about the RADARS that we talked about this morning is really interesting. And if Dr. Dart sees one of these come up on his

radar -- that's kind of a pun -- then that would be alarming. So that would be helpful. Yes, I don't envision any other human factors problems.

DR. ZACHAROFF: Thank you. Dr. Fischer?

DR. FISCHER: I agree with some of what Dr. Litman was saying. The REMS, I'm not totally convinced that the scope of the education that was proposed either by the applicant or FDA is that realistic, but was very reassured and actually thought it was commendable to do a very real-world human factors study in which people, it sounds like, may well not have read the directions but were still able to figure out how to use the device and not lose the pills. And that's quite reassuring to me that in -- it was only 45, as someone pointed out. But still in real-world use, the human factors concern is less so.

I think as it was well pointed out in the comments, we can come up with a story for a dropped pill, and I can understand the concern because one case like that could be incredibly problematic. But it seems like such a low probability that it

does not strike me as a reason to jump in the way of this kind of delivery system.

DR. ZACHAROFF: Thank you. Dr. Meisel?

DR. MEISEL: Well, I too have a few concerns. I do like the suggestion that, not only for this product but for other products before these committees where there's a delivery device you certainly need to get your hands on to get a feel for it, the hands-on is a lot better than the photos and we should be considering that in the future.

The one concern that I did have, and it was in the applicant's portion of the REMS to require that every hospital prospectively educate every nurse who may be using this product before they use it. I'm in an organization that's got 32,000 employees over 11 hospitals. I can't get my head around a system whereby I could guarantee that were to happen. We have nurses coming and going all the time with new hires and what-have-you with a million things they have to learn about how to run the electronic health record to do their timecards

to everything else. To try to throw this into it would be nothing more than a paper exercise and would be highly ineffective.

Now, the real-time stuff, the once in a while that you've got to use it, maybe this particular ED is going to use it a lot, so you're going to do some just-in-time training in your ED, that's a different scenario. But to try to come up with a system whereby you're prospectively educating every nurse who may have to use this just in case they do, I don't think that's practical.

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

MR. O'BRIEN: I commend the FDA on its efforts in terms of the human factors. I think the REMS portion does a good job. I would like to see it. And as I asked, I think a sample of the product would be very helpful for making decisions like that, even despite photographs.

I think that it's not isolated. I think the REMS plus with the sponsor indicating they are going to do the training -- and yes, there are a lot of things that hospitals and others have to do,

but we've got a major tragic epidemic on our hands here, and I would hope that any institution would understand that delivery of an opioid requires priority. So you're going to have to lift that up to make sure the people who are going to touch this, who are going to deliver it, do in fact get the training that they need in order to do that. Whether it's considered or perceived to be realistic or not, it's going to be required to do that.

So I think the hospital and the sponsor living up to their commitments to do training, plus with the REMS, I think the three of them gives us a tool of control that is reasonable in terms of mitigating the risks that are there.

DR. ZACHAROFF: Thank you. Dr. Higgins, did you have something to say?

DR. HIGGINS: Dr. Meisel stole my thunder.

DR. MEISEL: I'm sorry.

DR. ZACHAROFF: I'll just throw in my comment that I agree. I think the FDA is to be commended about doing the human factor evaluation.

And considering actually how a product like this would be used, I also very much, from a safe and effective use perspective, like the wording of hospitals, emergency departments, and surgical centers because that much more clearly defines where this medication might be used safely and effectively as opposed to the nebulous medically supervised setting wording.

Dr. Fischer, did you have something else?

DR. FISCHER: I think Greg.

DR. ZACHAROFF: Okay. Dr. Terman?

DR. TERMAN: Greg Terman from University of Washington in Seattle. I think that there's been a lot of evidence that this is very similar in terms of risks to other opioids. And with this REMS, I would say that it's even more safe than most other opiates used in the hospital.

I will admit that I was concerned about the hourly possibility of nurses having to go in and give multiple doses when in fact they've got lots of other patients to take care of, but nurses can be trained really well. I started when PCAs were

just coming into the hospital and epidurals have come into the hospitals. And although I don't see the niche for this particular product in the same way, the human factors study demonstrated that even with the instructions on the package, people can know what to do.

Although they're supposed to also be taught, it may be rare enough they'll be looking at those packages. But it sounded like even in damaged packages, after a little bit of experience in the human factors trial, people stopped looking at the packages and were able to do it just fine. So I think that the REMS really limit use perhaps appropriately but certainly safely.

DR. ZACHAROFF: Thank you. If there are no more comments or discussion, just a summary of what I captured. We heard from a number of people, it would have been nice to see the product just to get an idea of what it looked like, how it felt, and how small the pill actually was. We heard positive feedback by and large about the FDA proposed REMS, and we also heard concern that if this medication

did end up showing up in RADARS data, that that would be very concerning, indeed.

We heard positive feedback, almost universally, about the human factor evaluation that was done by the FDA, and we also heard that it might not be practical to train every single person in an institution who might be tasked with covering the patient or needing to care for a patient who might need to get a medication like this and that that could be challenging.

We heard that, by and large, most people felt that the risks of this particular opioid medication are probably in line with or less than those with other similar opioid medications. Then lastly, that education might not end up being a barrier based on the data provided that people were able to not read the directions and still end up giving the medication appropriately.

Did I get it?

(No response.)

DR. ZACHAROFF: Okay. So I'm taking this to mean that there are no further questions or

comments regarding this or other questions that we've addressed.

(No response.)

DR. ZACHAROFF: So then we will in a moment -- I'm sorry. We will tackle question 4. Discuss any concerns you may have regarding the abuse or misuse of sufentanil sublingual tablets and whether, based on the available data, the benefits to patients are expected to outweigh public health risks as they relate to abuse, misuse, and accidental exposure.

So just take a moment to look at the question. Let me know if there are any questions or comments regarding the wording of this question.

(No response.)

DR. ZACHAROFF: Okay. Then we will now open the question to discussion. Ms. Phillips?

MS. SHAW PHILLIPS: I think in terms of abuse, we've got the same concerns we would have with any other Schedule II substance that's in the hospital, so that's not my greatest area of concern. I think the area where I'm really toying

is the misuse, and thinking from a formulary perspective in our health system, really thinking about it potentially being used in areas where there's not enough good evidence that it's a suitable alternative or better alternative.

So again, I don't see this in a post-op setting. And as an IRB chair, I'm looking at how difficult it would be to do the studies that we would really need to show if it has a niche and a true public health benefit, which again is in that immediate first-dose situation when you're trying to treat somebody for initial pain management, and you don't have access to the IV.

I think that would be a challenging study to do without a community consent design or something like that, but that would be the next thing that I would be asking for to help weigh those things in a little bit more detail.

DR. ZACHAROFF: Thank you. Dr. Kaye?

DR. KAYE: Alan Kaye from LSU. I think the risk of abuse in the setting that it's been described is rather low, and I think that the

benefits largely outweigh the risks. It will find its own niche such as in settings like the emergency room and perhaps in palliative care, which we didn't really talk about today. But I do think that, largely, the benefits would outweigh the public health risks for abuse, misuse, and accidental exposure.

DR. ZACHAROFF: Thank you. Dr. Meisel?

DR. MEISEL: I too am not overly concerned about the abuse issues with this particular product. All opioids can be abused, and one will no doubt will be. The one unique feature about this that may make it just a little bit unique in this space of a hospital for somebody who wants to divert is that it is a tiny tablet. It's readily a dissolvable. Some nurse pretends to give it to a patient and then pockets that, and then puts it into a little bit of water or something, and nobody's the wiser.

I could see that happening. Will that happen commonly? Probably not. Will it happen to the extent that that's greater than other opioid

diversions? Probably not. But it's a unique way of diverting that probably doesn't exist with some of the other products. Again, I'm not overly concerned about it, but I think we just have to acknowledge that that potential is there.

I do agree that there's more of a risk of misuse than there is of abuse. Once this product is available, people will find all sorts of unique ways deciding to use it beyond labeling. There will be indications that nobody has dreamed up before; that even today, the sponsor would say, no, don't do it, people will find a way of doing it. And that will end up with all sorts of unintended consequences.

Now, that isn't a factor for approval or disapproval, but I think it's something we have to acknowledge that all drugs wind up being used off label, and when you have a drug as potent as sufentanil, the consequences of that can be very significant.

DR. ZACHAROFF: Thank you. Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. I am

not overwhelmed with the usefulness of this drug, however, I do believe that its benefits outweigh the risks based on its unique ability to be used sublingually. There are many questions still to be answered. Is this just as good as Motrin? It might be or there are other sublingual opioids that are to be used, and I would ask the FDA to carefully consider the difference between them.

So my guess, although I don't know the data, is it's a sublingual form of fentanyl. If this is really an unmet need that you need something in the emergency room to treat somebody before you get an IV in, well, there are a couple different forms of sublingual fentanyl or buccal. My guess is that Sufenta is less potent than those, and it might be safer, although not as effective.

So those are the kinds of things I would weigh. But because I don't see this as a public health risk or a safety issue, I do think its marginal benefits outweigh the risks.

DR. ZACHAROFF: Dr. Shoben?

DR. SHOBEN: I would agree with what's been

said, that as it's currently set up with the REMS in keeping it in hospital settings, that the risk for public health, unintended abuse, misuse, and accidental exposure risks are very minimal. I would stress that that's very much based on the assumption that it would stay in the hospital setting. Kicking it out to an in-home kind of place would both dramatically increase the risk of accidental exposure and potentially abuse since it's such an easily absorbed, potentially very abusable kind of delivery device.

DR. ZACHAROFF: Thank you. So to summarize, just to make sure I captured everything, it might actually be difficult to determine what the public health risk might be comparing it to benefit based on the fact that it's likely to be used in an institutional setting. It will likely find a clinical home.

In the context of that clinical setting, wherever it ends up being used, whether it's the emergency room or some other place in a hospital setting, we heard most members feel it's not likely

to increase the risk of aberrant behavior; that's despite the fact that we can always expect that that diversion is going to happen, and somehow or other, one way or another, somebody's going to figure out a way to get their hands on this medication and abuse it.

We thoughtfully heard that, actually, it might be the risk of misuse that may be the challenge more than abuse or accidental exposure because of the fact that people might still experience breakthrough pain and people might give it more frequently than they're supposed to. And then we heard emphasis on the fact that risk of abuse and misuse is probably low if it stays where it's intended to stay based on the discussion we have today.

Mr. O'Brien, did you have something to say?

MR. O'BRIEN: I do. Thank you. Sorry. From my perspective, in looking at it from what I've seen, I would almost say that I think the abuse particularly, it's probably safer. It's less tending. And I say that from actually being a

former director of white collar crime and director of audit in the sense that when you look at the human factor, you know how to package. It only has one unit in there, so it only has a very limited amount as opposed to stealing a bottle or something else where I'm going to get 100 to 200. Now I have to get a packet. I have to open up that packet. I have to take that out. I have to use it sublingually.

There are a lot of factors there that to me would seem to mitigate the abuse as compared to something else that I could get. If I'm going to spend my time and energy, I would steal something else to take that. So it would seem to be less than that.

I do see that for the targeted population. I don't see it myself. As I said, I don't think in the spine community -- I don't see it for me. I don't see how that would apply to that. I do see, in the case that I had mentioned, my own specific case in the ambulance and others that I've seen that are in acute pain, that if it's immediate, and

it's faster, and it's sublingual when they can't do it -- I do have caution -- I understand the need to keep it within the hospital, but I do think about our soldiers, and I do think about the battlefield, and I do think about the opportunity there that was expressed. And I think that's a very real need.

We heard from southern California very specific numbers in terms of 2600 people that come in, which is a third of those are over 65 and half of those can't use IVs. So there is a very real population that it appears for which there is a need and that this would apply. I have to rely on a lot of things for the doctors to do what they're going to do and apply. And sometimes that goes way off label and sometimes it doesn't, like everything else.

But it seems to me like there has been a true targeted needs that has been expressed for a certain population that's here, that this would provide -- this new novel delivery system would provide and answer that need. So from that perspective, I think the benefit overrules the

risk.

DR. ZACHAROFF: Ms. Phillips?

MS. SHAW PHILLIPS: I did want to follow up because I had the same questions that Dr. Litman did initially about we have fentanyl in a transmucosal formulation and we don't even use that in the hospital. But looking at that, that is only indicated for patients that are opioid tolerant. And if you look at the way the dosage form works in the lollipop, it's something that's more for chronic pain than -- it wouldn't be usable in the current formulation in the acute setting that we're talking about.

So I think there is still an unmet need for something that is more rapidly available sublingually than what we have on the market right now.

DR. ZACHAROFF: Okay. One more thing we're going to vote on before we actually vote, and that is we were scheduled to have a break at 3:00 p.m. and then come back and continue.

MALE VOICE: [Inaudible - off mic].

(Laughter.)

DR. ZACHAROFF: Okay. So the consensus is to carry on and go to the vote. I'm assuming there are no further questions or comments, and that means that we will begin voting in a moment. Just to let you know, we will be using an electronic voting system for this meeting. Once we begin the votes, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your or you wish to change your vote, you may press the corresponding button until the voting is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individually state how we voted and our name into the medical record. And you may also opt to state the reason why you voted as you did, if you'd like. We will continue

in the same manner until all questions have been answered or discussed before we adjourn.

I'm going to read the question at hand. Overall, do the benefits of sufentanil sublingual tablets, 30 micrograms with the REMS proposed by FDA outweigh the risks for the management of moderate to severe acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adult patients in a medically supervised setting, supporting approval of sufentanil sublingual tablets, 30 micrograms?

(Voting.)

DR. ZACHAROFF: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 10, yes; 3, no; and zero abstentions.

DR. ZACHAROFF: So let's go around the room. If we could start on this side of the table.

DR. MEISEL: Steve Meisel with Fairview. I voted no for a number of reasons, many of the reasons I've already stated. But I think in terms

of efficacy, I think the onset is too slow. That will lead to dose stacking and repeated doses.

The population that's being described is too broad. I can see this in an ED setting or battlefield situation, but in any other circumstance, the idea of not having an IV line, I don't see that indication. I don't see the value there. I see lots of risks in those settings.

No IV line means no IV naloxone, and I think that's a serious risk. We don't know what the equivalent doses are. I've never come across a opioid drug for approval that I can't tell you what the equivalency is in terms of morphine. The 30 milligrams equals 5 is highly inaccurate.

The issues of dose titration and flexibility I think are problematic. It will end up being used in ways that are unsafe and dangerous. The experience of the elderly is nonexistent. We have no idea how to dose it, if to dose it, and whether to give it all in the elderly. I think that's problematic.

A comment that probably doesn't really

relate to whether we should say yes or no or not, but I think needs to get into the record is that this product will create a tremendous amount of plastic in the waste stream.

From an environmental point of view, I think with all the plastic problems that we have in oceans and every place else, the amount of plastic for this product, for 1 dose of this product is extraordinary. And I think that's to me is a concern that doesn't lead to approval or disapproval, but I think it's something that we need to acknowledge.

MS. SHAW PHILLIPS: Marjorie Shaw Phillips. I voted yes, but with some qualifications, and that's really looking at some of the terms and language. And I had a lot of the same concerns that Dr. Meisel did, particularly for which alternative treatments are inadequate. And then I do see that benefit being in that narrow population for somebody that you want to give something immediately and your only other route is giving intranasal something off label or a product that's

not often available.

So I think having a sublingual product for that immediate use when there's no IV access is certainly reasonable. I also agree with Dr. Zacharoff about the term "medically supervised supervised setting" needing to be further delineated and stricter and have concerns about dose stacking and time to effective pain relief. But I think for at least a narrow indication, there are some populations where this does have a substantial risk-benefit profile because there aren't suitable alternatives.

DR. FISCHER: Mike Fischer, Boston. I voted no, and the reasons really focused more on the efficacy. I echo a lot of sentiments of the two panelists who already spoke. I was quite reassured about the safety and the REMS and human factors and so on. So for weighing risks versus benefits, that by extension means I was pretty underwhelmed with the efficacy, and that's especially in the populations without alternatives.

As Dr. Meisel pointed out, the argument that

was made was that this is for patients who need something very quick in these narrow windows where it's hard to get IV or another option, and we saw a relatively slow onset, which then to me begs the question so what exactly is the niche where this drug is most beneficial? And I didn't feel like I had enough data to answer that question positively.

DR. LITMAN: Ron Litman. I voted yes for the reasons I elaborated before. Just as a one liner, I think that ultimately if this drug gets approved, the ED physicians and the physicians in battle will determine its usefulness. And I wasn't concerned about the safety or public health.

DR. ZACHAROFF: This is Kevin Zacharoff. I voted yes pretty much for reasons that have already been stated.

DR. ZELTZER: Lonnie Zeltzer, and I voted yes. I think there's certainly a need in a very narrow population. And just a comment, if you give an oral med because you can't -- I mean, a swallowed oral med, not sublingual, because you can't get an IV, and you're in this same issue with

giving an opioid reversal agent. So I don't think that's unique to this. Anyway, I agree with the reasons said.

DR. SHOBEN: Abby Shoben. I voted yes. The benefit I think is actually fairly comparable to a lot of the other opioids that we've looked at and that they establish it and many of the same ways that we've seen it. That was pretty clearly demonstrated for me. And the risks especially with the REMS mitigating the risk of it being out in the community make the risk both to the individual patients and to the public health pretty minimal.

DR. KAYE: Alan Kaye, LSU. I voted yes. I think there are benefits to a certain population, and I think the risks certainly are satisfactory in my view the way that the product will be intended to be used.

DR. TERMAN: I'm Greg Terman from University of Washington in Seattle. I voted yes because, in my opinion, there was clear efficacy for acute pain and minimal risks, at most, the same as other opiates in the hospital. Also, it would fill a gap

in our current pharmacopeia for treating pain quickly without an IV. I was not convinced so far. I'm skeptical that that's actually going to be true, that fast onset may or may not be true based on the data, but that doesn't affect, for me, that it is efficacious and safe.

MS. WILLACY: Jacqueline Willacy. I voted no, and I admire a lot of your sentiment. I could see it in an ER environment or on the battlefield. In the acute care setting, I think it's going to be very taxing on the nurses. For the stacking, there's no titration process for this medication. It's hourly, and it's going to require a lot of monitoring.

A lot of patients, if you're not in the ICU setting or a step-down setting, you don't have continuous monitoring, so it's going to require more. From a nursing perspective, it will require nursing power, nursing hours, and just to keep going back and forth to look at the patient to make sure you're safe. I wouldn't recommend it for an inpatient. Just about all our inpatients do have

an IV.

DR. WARHOLAK: Terri Warholak, and I voted yes for reasons stated before that I will not elaborate on. But while I have the microphone, I wanted to commend the FDA for the good work that you do. I don't think that many people in the public know what you do or the lengths you go to do it. And I've always been, every time I come here, very impressed with the work that you've done. Not only do you provide thoughtful reviews of the sponsor's data, but you always do, or often do, methodologically rigorous studies in-house as well, and I don't think people know a lot about that, so thank you.

DR. HIGGINS: Jennifer Higgins. I voted yes, I guess maybe surprisingly to some people. I was persuaded by the data in totality. What I would suggest, though, is specific label language. I would like to see something in there about caution to be used with older adults with this medication. I'd also like to see the sites -- just like Dr. Zacharoff said, I'd like to see the site

spelled out. It could be something like where intravenous opioid medications are already being used or hospitals. I think it should be spelled out, is what I think.

MR. O'BRIEN: Joe O'Brien, and I voted yes. I wish I was voting yes to eliminate all opioids, but it's a real world, and I think it behooves us to do a better job at what we do. I think this is one step to doing a better job for a very niche patient population who has a need, so I support that effort.

I also want to very much thank the FDA. It is always a pleasure, and I think it was a great job with what you did and what you always have to do in terms of working with the sponsor to try to work it out. And it's very evidenced by the struggle we have around here to try to come to the decisions that you have to come, and I thank you for that.

DR. ZACHAROFF: I would like to say from the FDA perspective that the presentations today from the FDA I think really helped the committee a

tremendous amount to come to the conclusions and create a lot of thoughts. So spectacular job on the people who presented today.

Before we adjourn, I'd just like to ask if there are any last comments from the FDA.

Dr. Hertz?

DR. HERTZ: Well, I would like to say how much I appreciate the time and effort you all put in. We keep dragging people across the country. Thank you, Dr. Terman and others. And we know it's no small thing to take time from what I appreciate to be very, very busy lives. So thank you; always helpful.

Adjournment

DR. ZACHAROFF: As we adjourn, panel members, I just want to remind you to please take all personal belongings with you as this room is cleaned and emptied at the end of each meeting day. Any materials left on the table will be disposed of. Please also remember to drop off your name badge at the registration table on your way out so they may be recycled, and we will now adjourn this

meeting. Thank you.

(Whereupon, at 3:03 p.m., the meeting was adjourned.)