Introduction and Review of Clinical Safety and Efficacy

New Drug Application (NDA) 209128

Sufentanil Sublingual Tablet (SST) 30 mcg

Anesthetic and Analgesic Drug Products

Advisory Committee Meeting

October 12, 2018

Ning Hu, MD, MS

Clinical Reviewer

Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Office of Drug Evaluation II (ODE-II), Office of New Drugs (OND), CDER, FDA

Overview of FDA Presentations

- **Introduction and Review of Clinical Safety and Efficacy**
  - Ning Hu, MD, MS
    Clinical Reviewer
    DAAAP, ODE-II, OND, CDER, FDA
- **Human Factors Evaluation**
  - James Schlick, MBA, RPh
    Reviewer
    Division of Medication Error Prevention and Analysis (DMEPA)
    Office of Medication Error Prevention and Risk Management (OMEPRM)
    Office of Surveillance and Epidemiology (OSE), CDER, FDA
- **Risk Evaluation and Mitigation Strategies (REMS) Considerations**
  - LaShaun Washington-Batts, PharmD
    Reviewer
    Division of Risk Management (DRISK), OMEPRM, OSE, CDER, FDA
- **Benefit/Risk Considerations**
  - Ning Hu, MD, MS

Presentation Overview

- Introduction
- Efficacy
- Safety

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- Safety

Overview

- **Drug name, class, and dosage form:**
  - Sufentanil sublingual tablet (SST), 30 mcg (proposed trade name Dsuvia)
  - Opioid analgesic, Schedule II

- **Combination drug/device**
  - Small tablet (3 mm in diameter and 0.85 mm in thickness) in a single-dose applicator (SDA)

Applicant's Proposed Indication and Dosing

- **Applicant's proposed indication:**
  - Management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting

- **Dosing:**
  - 30 mcg sublingually as needed with a minimum interval of one hour between doses
  - Do not exceed 12 tablets in 24 hours
  - Given by a healthcare provider in a certified medically supervised setting

Issues for Consideration

- Efficacy of SST 30 mcg for the management of acute pain
- Safety profile of SST 30 mcg
- Risk of misplaced tablets and risk of accidental exposure
- Overall benefit/risk considerations for SST 30 mcg

Key Regulatory Interactions: SST 30 mcg

- **October 4, 2011:** IND 113059 submission
- **December 12, 2016:** Original NDA submission
- **October 11, 2017:** Complete Response letter issued
  - The letter outlined two deficiencies:
    - Inadequate number of patients dosed at the maximum dosing proposed for labeling
    - Risk of misplaced tablets
- **January 26, 2018:** Post-action meeting to discuss the deficiencies and the Applicant's proposal to address them
- **May 3, 2018:** NDA resubmission

IND=Investigational New Drug

SST 15 mcg program

- SST 15 mcg is a different sufentanil-device combination (proposed trade name Zalviso)
- NDA received a complete response in 2014 primarily due to device-related issues
- Key differences between SST 15 mcg and 30 mcg:
  - Different devices
  - SST 30 mcg is administered by a health care provider while SST 15 mcg is administered by a patient
  - Different doses (30 mcg vs. 15 mcg)
- The Applicant used selected safety data from the SST 15 mcg program to support the SST 30 mcg program
  - Bioequivalence established between two doses of SST 15 mcg administered within 20 to 25 minutes and a single dose of SST 30 mcg

Overview of Data Supporting the SST 30 mcg Application

- 505(b)(2) NDA
  - References listed drug: Sufenta (sufentanil citrate for injection; NDA 19050)
- SST 30 mcg program
- Selected safety data from SST 15 mcg program

SST 30 mcg Clinical Studies

- Studies included in FDA's analysis
  - SAP 101: Phase 1 pharmacokinetic study
  - SAP 301: Phase 3 multicenter, randomized, placebo-controlled study
  - SAP 302: Phase 3 multicenter, open-label study
  - SAP 303: Phase 3 multicenter, open-label study

- Data from SAP 202 were not used to support the efficacy and safety of SST 30 mcg
  - SAP 202 used a different formulation and the in vitro data were not sufficient to bridge it to the final to-be-marketed formulation

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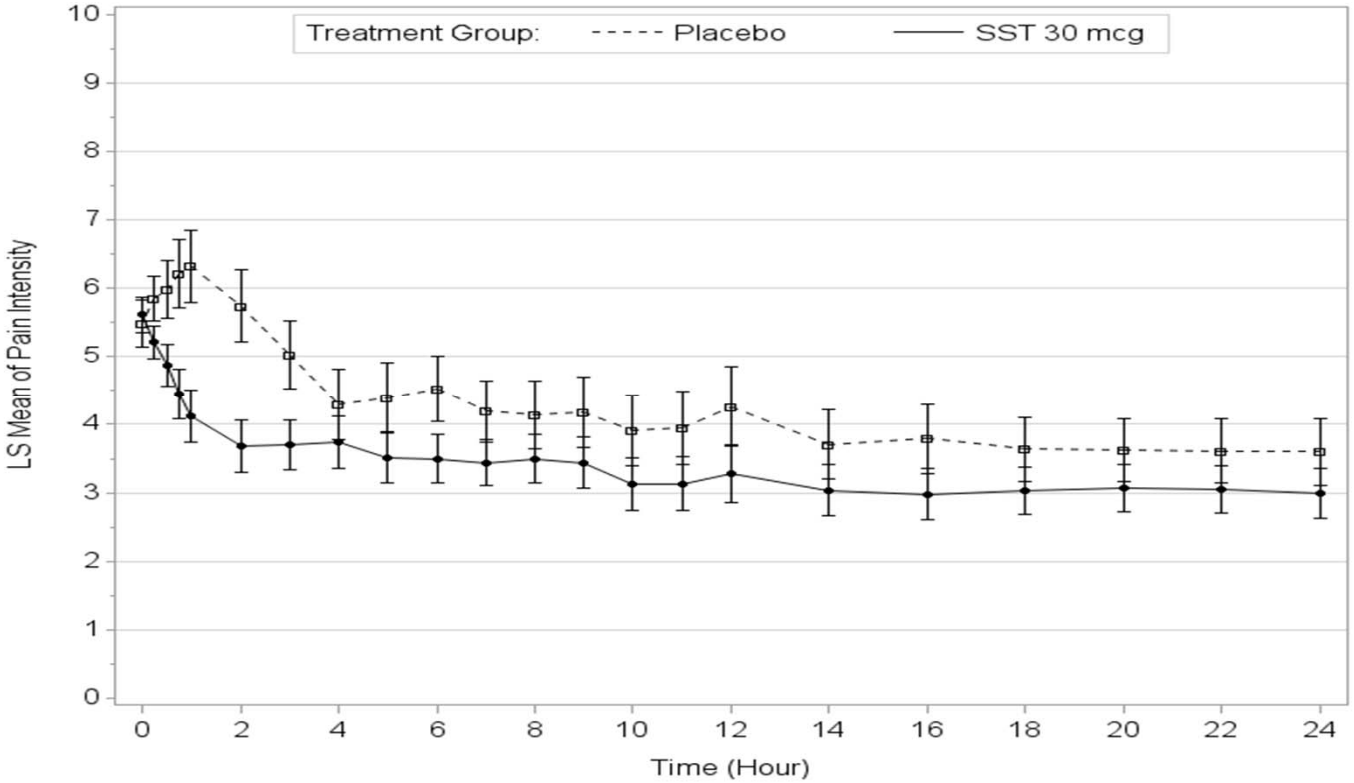
Overview of Study SAP 301

Characteristics	SAP 301
Design	• Multicenter, randomized, placebo-controlled
Treatment groups (# of patients)	• Sufentanil sublingual tablet 30 mcg (107) • Placebo (54)
Dosing regimen	• As needed per request with a minimum of 60 minutes between doses
Rescue analgesia	• Morphine IV 1 mg
Study duration	• Up to 48 hours
Study population	• Post-surgical adult patients pain intensity of ≥4 following abdominoplasty, open inguinal hernioplasty, or laparoscopic abdominal surgery
Efficacy measurement	• 11-point numerical pain rating scale (NPRS)
Primary efficacy endpoint	• Time-weighted summed pain intensity difference from baseline over 12 hours (SPID12)
Selected secondary efficacy endpoints	• Total number of study medication and rescue medication doses used over 12-hour study period • Time to onset of meaningful pain relief

Pain Intensity Scores Over 24 Hours: SAP 301 (ITT Population)



SPID12

Mean Difference (95% CI)	P-value
12.7 (7.2, 18.2)	< 0.001

Number of Rescue Medication Doses Used Over the First 12-Hours: SAP 301 (ITT population)

Number of Doses Used over 12 Hours	SST 30 mcg (n = 107)	Placebo (n = 54)	P-value
Mean (SD)	0.4 (1.0)	1.6 (1.8)	
Median	0	1	
Range	(0, 7)	(0, 8)	
LS Mean Difference (vs placebo)	-1.2 (-1.6, -0.8)		< 0.001

- 22% (SST 30 mcg) vs 65% (placebo) of patients used rescue medication in the first 12 hours

Time to Onset of Meaningful Pain Relief: SAP 301 (ITT population)

Time to Onset (minutes)	SST 30 mcg (n = 107)	Placebo (n = 54)
Median (95% CI)	54 (42, 72)	84 (56, 250)
Range	4, 2400	6, 606

Efficacy Summary and Conclusions

- The primary and secondary endpoints in SAP 301 support the efficacy of SST 30 mcg for the management of acute pain
- The efficacy of SST 30 mcg was compared to placebo

Presentation Overview

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Overview of Safety

- Evaluation of SST 30 mcg
  - Safety database included data from three SST 30 mcg studies and selected data from six SST 15 mcg studies

- Evaluation of device/misplaced tablet risk
  - Human factors studies
  - Risk assessment following accidental exposure to SST 30 mcg

Review of Safety: Original NDA

- **Sufentanil Exposure**
  - Total of 646 patients exposed to SSTs
    - 323 patients exposed to SST 30 mcg
      - 86% used fewer than six doses in the first 12 hours, and the remaining 14% used between 6 to 12 doses (SAP 301)
    - 323 patients exposed to SST 15 mcg
  - The overall size of the safety database was adequate for the 505 (b)(2) application. However, the number of patient exposed to multiple doses was not adequate.
- **Misplaced tablets**
  - Three events of dropped tablets in SST 30 mcg Phase 3 trials
  - Errors occurred in the first human factors validation study

Safety Review of SAP 301

- No deaths occurred
- **SAEs:** Two occurred in the placebo group
- **Discontinuations due to AEs:** Higher in the placebo group (3.7%) compared to the SST 30 mcg group (0.9%)
- **Common AEs:** The events in the SST 30 mcg treatment group were consistent with an opioid's safety profile
- **Respiratory:**
  - More patients had oxygen saturation < 93% in the SST 30 mcg group than in the placebo group (7.5% vs. 0% for SST and placebo, respectively)
  - Two patients in the SST 30 mcg group had oxygen saturations less than 92%

Deficiencies in Original NDA Review (1)

- **Inadequate number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of SST 30 mcg**
  - Important as there is a nearly 4-fold increase in exposure and a more than 2-fold increase in the maximum concentration when dosed at steady state
  - To address the deficiency: collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety following the maximum dosing proposed

Applicant's proposal to address this deficiency:

- Decreased the maximum daily dose from 24 to 12 tablets and submitted new pooled safety analyses

Deficiencies in Original NDA Review (2)

- **The possibility of misplaced tablets poses a potential risk for accidental exposure and improper dosing**

  – To address the deficiency: develop mitigation strategies to address the risk of dropped tablets and conduct another human factors validation study

  Applicant's proposal to address this deficiency:

  – Performed a second human factors study after incorporating the FDA's recommendations
  – Submitted a risk assessment following accidental exposure to SST 30 mcg

Applicant's Pooled Safety Analysis to Support Proposed Maximum Dose

- Pooled data from one SST 30 mcg study (up to 48 hours) and three SST 15 mcg studies (up to 72 hours)
- Analyses were based on total sufentanil dose received (<300 mcg or ≥300 mcg)
  - There are limitations to these safety analyses, such as:
    - Differences in the SST 15 and 30 mcg clinical programs
    - A variety of factors influence total dose received
  - Despite these limitation, there was no clear relationship between higher total sufentanil dose received and adverse events

Safety Concern Associated with Dropped/Misplaced Tablets

- **Significant safety concern of accidental exposure, overdose, and death, particularly in children**
  - Sufentanil is a Schedule II opioid
  - Small tablet size
- **To address this safety concern:**
  - Risk assessment following accidental exposure to SST 30 mcg
  - Two human factors validation studies
  - Risk Evaluation and Mitigation Strategies (REMS)

Risk Analysis Following Accidental Exposure to SST 30 mcg

- **Applicant predicted the sufentanil plasma concentration following accidental exposure**
  - FDA agrees with the Applicant's methodology
- **Applicant considered clinical implications of the predicted plasma concentration**
  - There are limitations in using the published literature to evaluate the risks associated with accidental exposure
  - While definitive conclusions are not possible, there is a risk of respiratory depression and death associated with accidental exposure

Summary

- SST 30 mcg was effective in reducing pain intensity in one placebo, controlled trial
- Safety profile of SST 30 mcg was consistent with an opioid agonist
  - However, given the small size of the sufentanil tablet, there is concern for risks associated with misplaced tablets, such as accidental exposure and respiratory depression

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Human Factors Evaluation

New Drug Application (NDA) 209128
Sufentanil Sublingual Tablet 30 mcg
Anesthetic and Analgesic Drug Products Advisory Committee Meeting
October 12, 2018

Otto L. Townsend, Pharm D

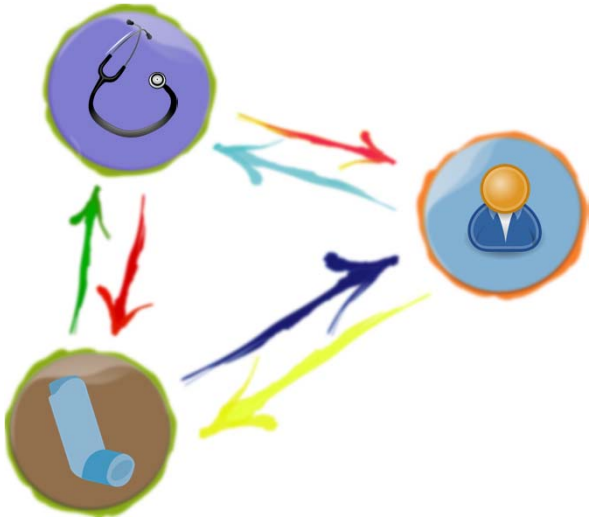
Team Leader
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE), CDER, FDA

Objectives

- Provide an overview of human factors engineering and its role in the development of medical products
- Describe the product characteristics for the sufentanil single-dose applicator
- Summarize the results from the human factors testing conducted for the combination product

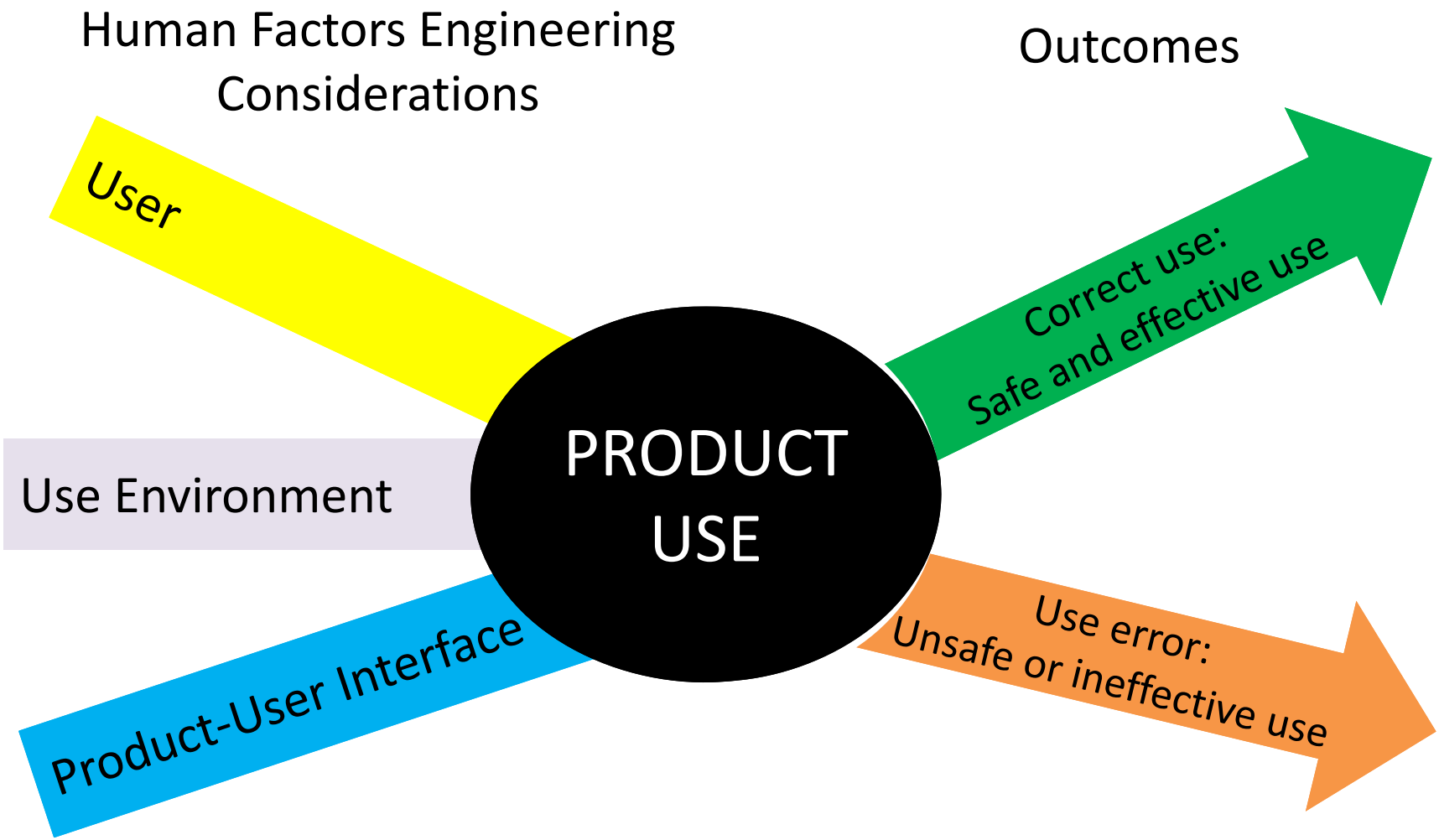
What is Human Factors Engineering (HFE)?

Ergonomics (or human factors engineering) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance.

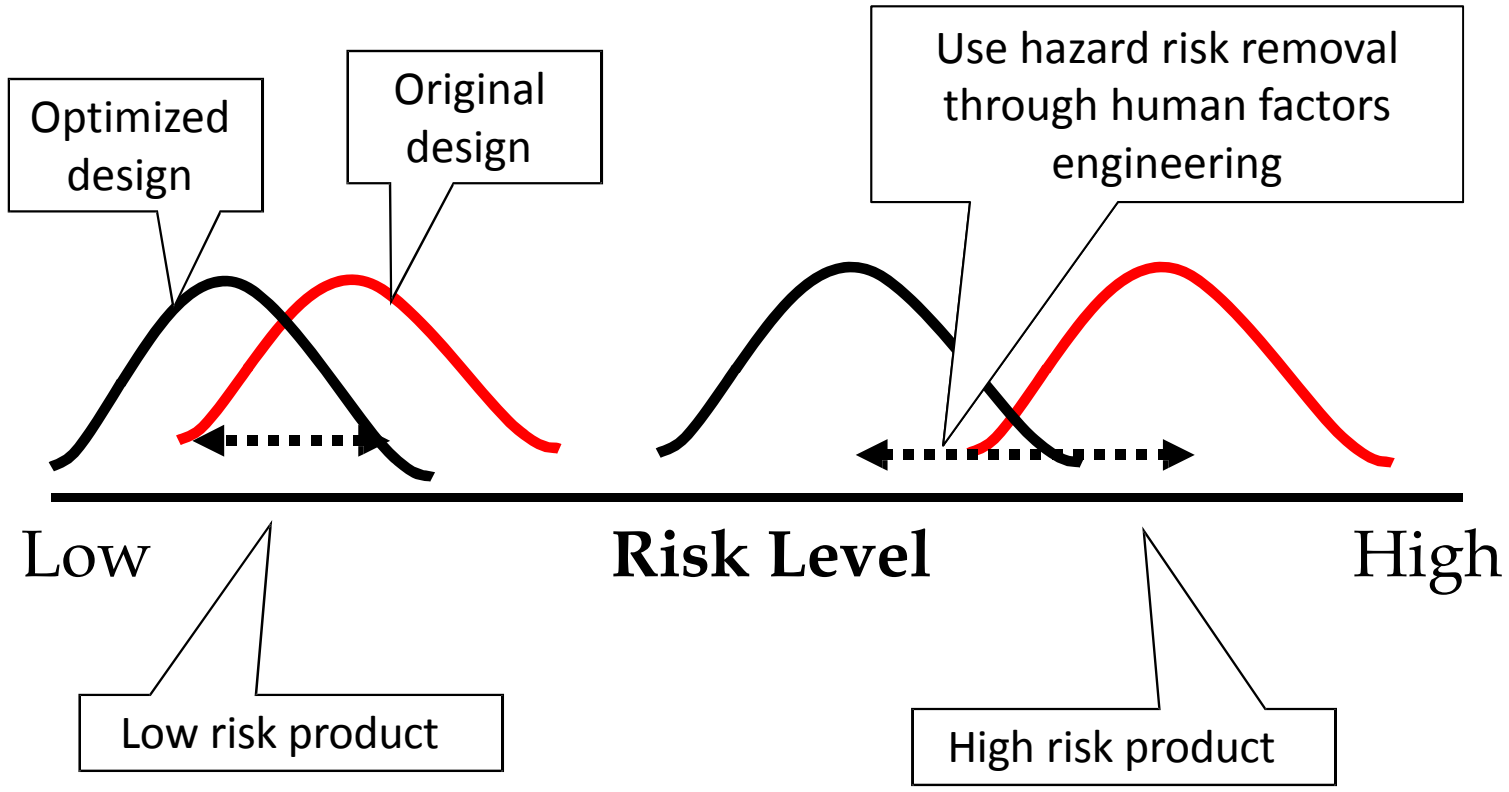


International Ergonomics Association (IEA)

Human Factors Engineering of Product Use



Goal of Human Factors Engineering in Product Design



Simulated-Use Human Factors Validation Testing

- **Objective:** Demonstrate that the combination product can be used safely and effectively by the intended users, for its intended uses, and intended use environments.
- **Design:** 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
  - The product user interface represents the final to-be-marketed design
  - The test conditions simulate real-world use conditions
- **Data**: Collected and analyzed to determine whether the objective was met.

Sufentanil Single-Dose Applicator (SDA)

The single-dose applicator tip goes under the patient's tongue, the green pusher is depressed by the HCP to administer the tablet to the sublingual space.

Photo Source:

FDA Advisory Committee Briefing Document for Sufentanil Sublingual Tablets. Sep. 10, 2018; pg. 89

HF Related Regulatory History

Date	Submission/DMEPA's Involvement
December 2015 to February 2016	- The Agency recommended AcelRx conduct an HF validation study and we reviewed their HF validation study protocol.
December 2016	- The Agency reviewed the HF validation study results report. - We requested that additional changes be made to the Directions for Use (DFU) and protocol. - AcelRx to provide additional HF validation data to support the implemented changes
November 2017	- The Agency reviewed the revisions made to the user interface and reviewed the new HF validation study protocol.
May 2018	- The Agency reviewed the second HF validation study results report.

First Validation Study – Submitted in Dec. 2016

Objective

- Aimed to test participant's ability to safely and accurately administer a sufentanil sublingual tablet using the single-dose applicator.

Participants

- 45 healthcare providers (HCP) participated
  - 15 Post-Anesthesia Care Unit (PACU) nurses/floor nurses
  - 15 ER nurses
  - 15 paramedics
- Live mock patients (not required to complete tasks)

Study Environment

- Simulated Emergency Room

First Validation Study Design (2016)

Design	**1. Training** • HCPs were requested to read the Directions for Use (DFU) before conducting use tasks **2. Use Tasks** • HCPs administered products 4 times (4 use scenarios) • HCPs had access to the Directions for Use (DFU) and instructed to read the DFU before proceeding **3. Directions for Use (DFU) Knowledge Questions** • Each participant answered 8 knowledge questions after completion of use tasks **4. Post-session interview** • Moderator conducted a post-session interview with each participant

Summary of First Validation Study Results (2016)

Study Sub-Tasks with Errors	Results
Places the single-dose applicator tip under the patient's tongue, into the sublingual space	2 errors - Participants thought the tablet was not housed within the single-dose applicator and were testing applicator only
Depresses the pusher to deliver the tablet to the patient's sublingual space	2 errors - Dropped tablets
Confirmation of tablet placement in the patient's sublingual space	8 errors - Did not confirm placement of the tablet (n=6) - Misunderstood the question (n=2)

DMEPA's Conclusion – First Validation Study (2016)

- We determined the data **did not** demonstrate that the user interface supports safe and effective use of the product by intended users, for the intended uses, and intended use environments.
- 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 the foil pouch.
- Conduct a human factors validation study to evaluate the changes implemented in the user interface.

Comparison of Differences Between Human Factors Validation Study Designs

Design Element	Validation Study #1 (2016)	Validation Study #2 (2018)
Training	HCPs were requested to read the Directions for Use (DFU) before conducting use tasks	HCPs were untrained and were not requested to read the Directions for Use before conducting use tasks
Study Environment	Simulated Emergency Room	Simulated single exam room with one hospital bed

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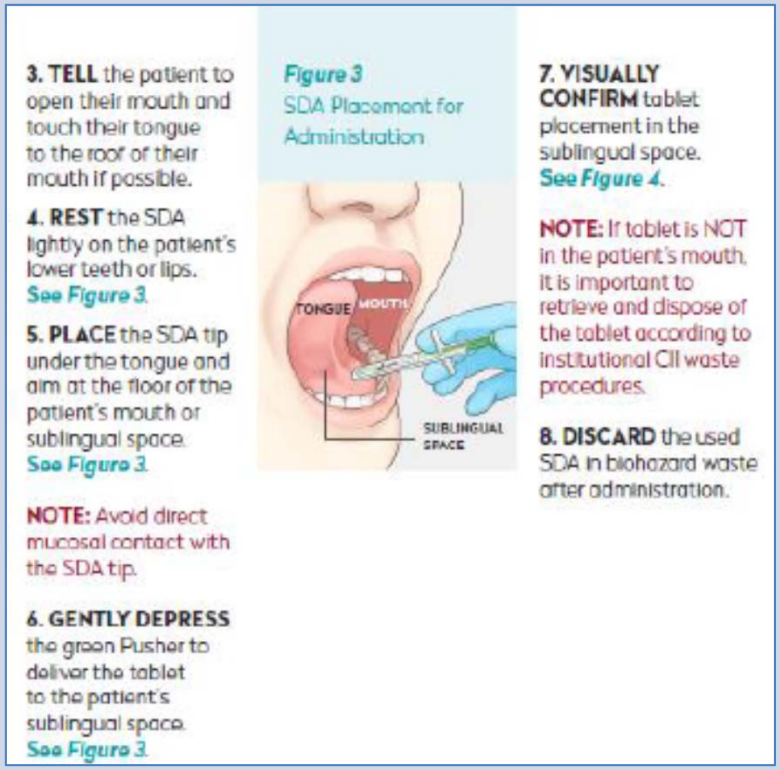
Changes Made to the Product User Interface After the First Validation Study

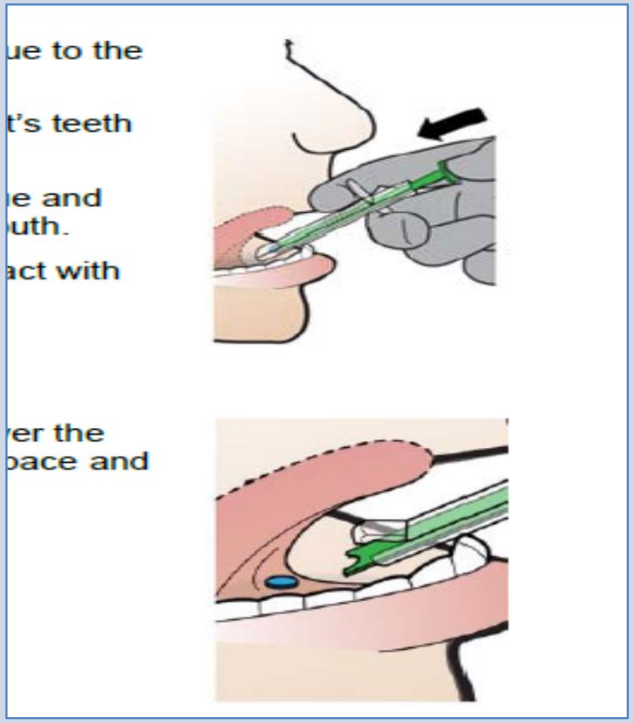
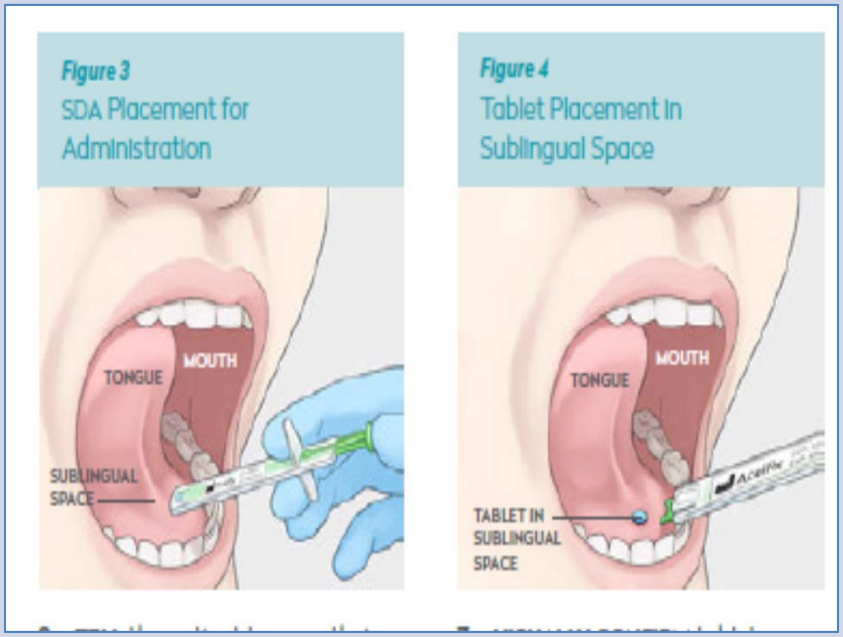
Changes to the Product User Interface

Revision of Step 6

Directions for Use Tested in First Validation Study	Directions for Use Tested in the Second Validation Study
6. Depress the green Pusher to deliver the tablet to the patient's sublingual space and confirm tablet placement. 7. Discard the used SDA.	

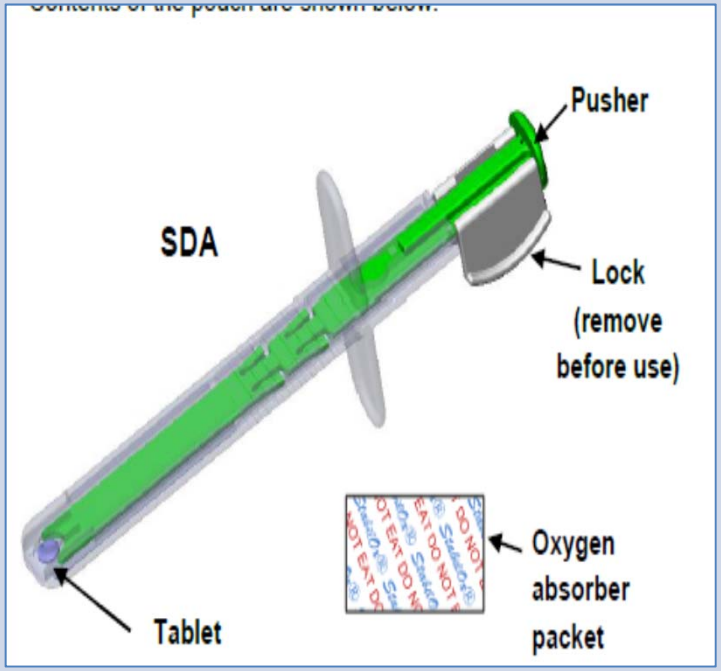
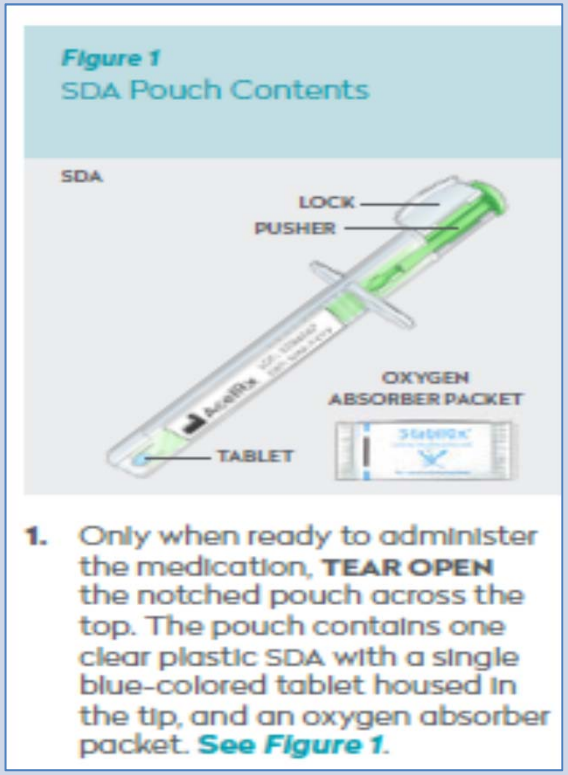
Changes to the Product User Interface

Revisions to Mouth Anatomy Figures

Directions for Use Tested in First Validation Study	Directions for Use Tested in the Second Validation Study
	

Changes to the Product User Interface

Label Each Figure

Directions for Use Tested in First Validation Study	Directions for Use Tested in the Second Validation Study
	

Changes to the Product User Interface

Attach Full Directions to Each Pouch

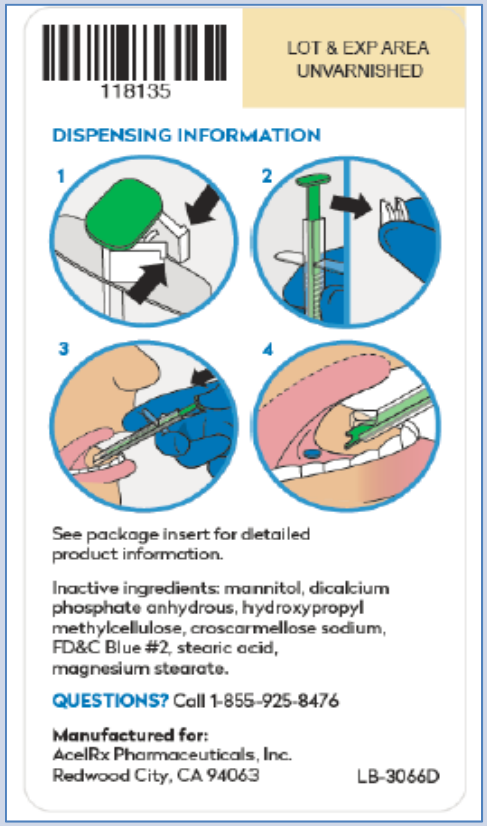
Quick Guide Tested in First Validation Study	Directions for Use Tested in the Second Validation Study
	

Photo Source:
FDA Advisory Committee Briefing Document for Sufentanil Sublingual Tablets. Sep. 10, 2018; pg. 11

Summary of Second Validation Study Results (2018)

- All tasks were completed successfully and there were no dropped tablets.

DMEPA's Conclusion

- Based on the data from this study, we have determined the design of the product user interface has been demonstrated to support the safe and effective use of the product by the intended users, for its intended uses, and intended use environments.

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Risk Evaluation and Mitigation Strategies (REMS) Considerations

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LaShaun Washington-Batts, PharmD
Reviewer
Division of Risk Management
OMEPRM, OSE, CDER, FDA

Overview

- Risk Evaluation and Mitigation Strategies (REMS) overview
- Risks associated with sufentanil sublingual tablet 30 mcg
- Risk management options:
  - Applicant proposal
  - FDA proposal

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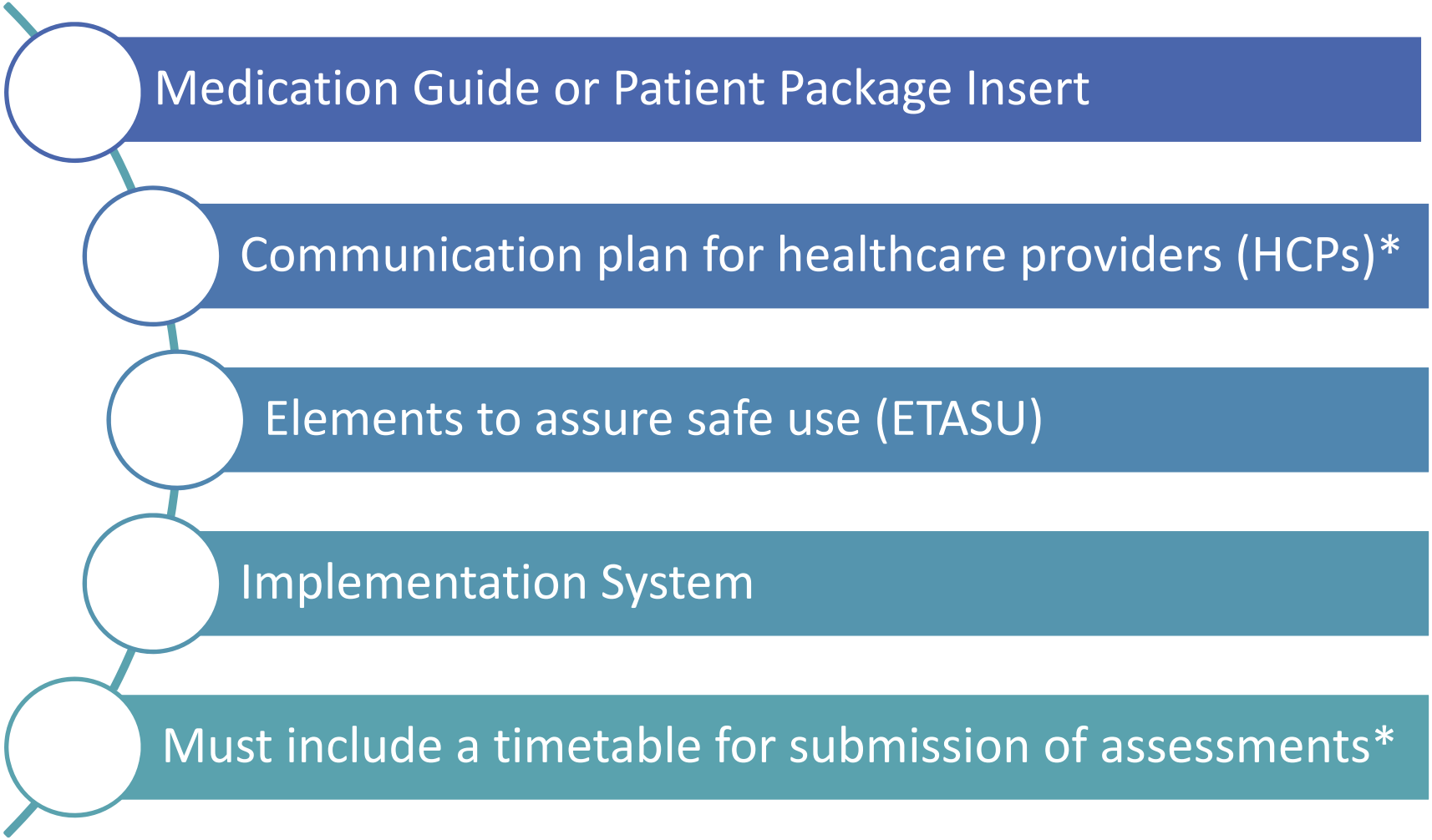
REMS Overview

A REMS is a Drug Safety Program that FDA Can Require for Certain Drugs

- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.
- REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
- The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require Applicants or Application holders to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
- The FDA has authority to require a REMS pre-approval or post-approval.

A REMS can Include a Number of Components



* *This requirement only applies to NDAs and BLAs.*

A REMS can Include Any of the Following ETASUs if Determined Necessary.

- Certification and/or specialized training of **HCPs** who prescribe the drugs
- Certification of pharmacies or other dispensers of the drug
- Dispensing/administration of drug in **limited settings**, e.g., hospitals
- Each patient using the drug is subject to certain **monitoring**
- Drug is dispensed/administered only with **evidence of safe-use conditions**, e.g., pregnancy test
- Enrollment of treated patients in a **registry**

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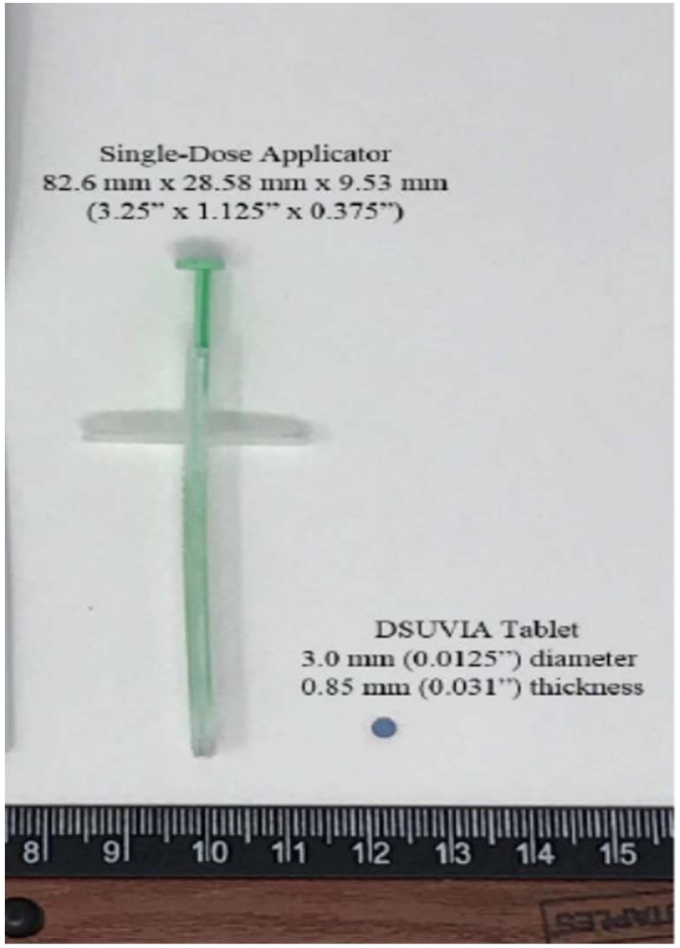
Risks Associated with Sufentanil Sublingual Tablet 30 mcg

Sufentanil Sublingual Tablets 30 mcg are Very Small

- The tablet is 3 mm in diameter and requires an applicator to administer the drug.
- Its small size presents a risk of dropping or misplacing the tablet during administration.
- Accidental exposure, particularly in children, can lead to respiratory depression, overdose, and death.
- Similar to other opioids, it carries the risks of misuse, abuse and addiction.



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The Applicant has proposed a REMS with ETASU to mitigate the risks of sufentanil sublingual tablets 30 mcg

The Applicant's Proposed REMS Goal

The goal of the proposed REMS for sufentanil sublingual tablet 30 mcg 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 REMS has the Following ETASUs

- Healthcare facilities and services that dispense sufentanil sublingual tablets 30 mcg are certified.
  - An authorized representative enrolls on behalf of the healthcare facility or service.

- Sufentanil sublingual tablet 30 mcg can only be dispensed to patients in medically supervised settings.

In the Applicant's Proposed REMS, the Responsibilities of an Authorized Representative Include:

Oversight of implementation/compliance with the REMS Program requirements by:

1) Reviewing the following:
   - REMS materials - Safety Brochure and Dear HCP Letter
   - Prescribing Information

2) Acknowledging the healthcare facility or service qualifies as a medically supervised setting by having:
   - a licensed pharmacy or HCP with DEA registration for CII drugs who will oversee ordering and administration of the medication;
   - access to equipment and personnel trained to detect and manage hypoventilation, including use of supplemental oxygen and opioid antagonists, such as naloxone.

In the Applicant's Proposed REMS, the Responsibilities of an Authorized Representative Include: (cont'd)

Oversight of implementation/compliance with the REMS Program requirements by:

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

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

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FDA's Proposed REMS

The FDA's Proposed REMS Goal

The goal of the sufentanil sublingual tablet 30 mcg REMS is to mitigate the risk of respiratory depression resulting from accidental exposure by:

- Ensuring that sufentanil sublingual tablet 30 mcg is dispensed only to patients in certified medically supervised healthcare settings.

The FDA's Proposed REMS

To become certified to dispense sufentanil sublingual tablet 30 mcg, each medically supervised healthcare 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.
- Train all relevant staff involved in administration to refer to the *Directions for Use (DFU)* prior to administration.

The FDA's proposed REMS includes a few differences from the Applicant.

The Differences Between the FDA and Applicant Proposed REMS

- FDA's proposal focuses is on the risk of respiratory depression resulting from **accidental exposure**, not **inappropriate administration**.

- FDA's proposal limits the use of the drug to a certified medically supervised healthcare setting. The Applicant proposes its use in certified healthcare facilities and **services**.

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Benefit-Risk Considerations for SST 30 mcg (1)

Benefits

- The primary and secondary endpoints support the efficacy of SST 30 mcg for the management of acute pain
- SST 30 mcg would provide another option for the treatment of acute pain in a medically supervised setting

Benefit-Risk Considerations for SST 30 mcg (2)

Benefits

- The primary and secondary endpoints support the efficacy of SST 30 mcg for the management of acute pain
- SST 30 mcg would provide another option for the treatment of acute pain in a medically supervised setting

Risks

- Opioid-class related AEs, such as:
  - Respiratory depression, addiction, abuse, misuse, accidental exposure, and gastrointestinal events
- Product specific risks due to the small tablet size of a Schedule II opioid
  - Amplifies risks related to accidental exposure, misuse, and abuse

Benefit-Risk Considerations for SST 30 mcg (3)

Benefits

- The primary and secondary endpoints support the efficacy of SST 30 mcg for the management of acute pain
- SST 30 mcg would provide another option for the treatment of acute pain in a medically supervised setting

Risk Management

- REMS with ETASU that focuses on the risks of accidental exposure

Risks

- Opioid-class related AEs, such as:
  - Respiratory depression, addiction, abuse, misuse, accidental exposure, and gastrointestinal events
- Product specific risks due to the small tablet size of a Schedule II opioid
  - Amplifies risks related to accidental exposure, misuse, and abuse


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