

# **Regulatory Issues in Pain Management: What everyone needs to know!**

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# Objectives

- Describe the current issues related to regulatory standards in pain management.
- Identify the importance of the REMS regulatory program related to pain management.

# Definition of Regulation:

A law, rule or order  
prescribed by authority.

**SAFE  
ACCESS**

**ASSURE  
SAFE USE**

Mandatory registry  
Nurse Training  
Technology to collect data lab  
results, patient health measures  
Documentation of patient monitoring

**ASSESSMENTS & MONITORING**

Health management • Voluntary patient registry  
Assessments • Therapy compliance and adherence  
Integrated systems with pharmacy dispensing data

**ENHANCE COMMUNICATIONS**

Pharmacist education/counseling • 24/7 Clinical support • Training  
Nurse training, education, and clinical services

**Regulatory Compliance:**  
It's time-consuming and  
expensive to comply with  
legislative and regulatory  
requirements

## Carol Gentry Health News Florida



### Florida Candy

Regulations on Florida pain-management clinics that will impose an estimated \$65 million in costs on the private sector passed the Florida Board of Medicine unanimously last week, despite Gov. Rick Scott's [edict to ban rule-making](#) this year.

Board members asked their staff to send letters to both the Legislature and the governor's Office of Fiscal Accountability and Regulatory Reform, explaining the need for immediate implementation of these rules, given the significant threat to public health and safety that some "[pill mills](#)" have created in the state. The four rules adopted on Friday set out the requirements for standards of care, inspections, accreditation and training in pain-management practices.

The \$65 million in estimated cost derives almost entirely from the requirement that clinics perform periodic urine screens. The Department of Health commissioned the study after the Legislature required them for all pending rules with at least a \$200,000 impact on business.

Paul Sloan, a clinic owner in southwest Florida who helped the Center gather information, said he knew the total would be substantial, but even he was surprised.

# Pain-Evidence Based Treatment Guidelines

- World Health Organization Three Step Analgesic Ladder
- American Pain Society's Quality Improvement Guidelines for the Treatment of Acute Pain & Cancer Pain
- ASCO's Cancer Pain Assessment & Treatment Curriculum Guidelines
- National Comprehensive Cancer Network Pain Guidelines
- Oncology Nurse Society's Position Paper on Cancer Pain
- AHCPR Clinical Practice Guidelines No. 9: Management of Cancer Pain
- ASA Guidelines

# DEA Drug Scheduling

# Schedule I

- Illegal/restricted to research, high abuse potential; no accepted medical use in US
- Examples: hallucinogens, heroin, cocaine and marijuana



# Schedule II prescriptions

- Prescription only, high abuse potential
- No need for specialized script, DEA # only
- 30 day or less supply only, no refills
- Can give limited quantity, ex. 2 weeks only
- Cannot be called or faxed in
- Patient or family must show ID on pick up
- 60 day expiration of script

# Schedule II cont.

- Check availability at pharmacy
- Examples: amphetamines (Ritalin®), barbiturates, opioids (single entry, some combos)
- Percocet
- Patient and family teaching is key-safe keeping of medications

## **FDA Approves Morphine Sulfate Oral Solution for Relief of Acute and Chronic Pain**

*Approval is part of Agency's unapproved drugs initiative*

The U.S. Food and Drug Administration approved Morphine Sulfate Oral Solution for the relief of moderate to severe, acute and chronic pain in opioid-tolerant patients. This medicine will be available in 100 milligrams per 5 mL or 20 milligrams per 1 mL.

This is the only FDA approved morphine sulfate oral solution available at this concentration. Although the use of this medicine to manage pain has been common practice for many years, this form and concentration of morphine was not FDA approved until now.

Today's action is part of the FDA's unapproved drugs initiative. As part of this program, the FDA has worked with the manufacturer of the now-approved product, Roxanne Laboratories, to ensure that there is enough drug available for patients. The FDA will also be working with patient organizations and prescribers so that they are aware that an approved product is available, and can notify the FDA if there are any problems with availability.

“An important goal of the unapproved drugs initiative is to make sure that marketed drugs meet current FDA standards,” said Douglas Throckmorton, M.D., deputy director for the FDA’s Center for Drug Evaluation and Research. “Our action today reflects a careful balance between ensuring patient access to necessary medicines, while making sure companies comply with the law.”

One benefit of the FDA approval process is a requirement for manufacturers to provide sufficient information on how to safely prescribe and use a drug. Manufacturers may also have to establish additional safety measures to manage unique risks of a medicine. **For this formulation of morphine, the manufacturer had to develop a safety program prior to approval to address the known risks of morphine misuse, abuse and overdose.**

# NP prescribing of Controlled Substances

- Valid DEA Registration Number
- Comply with requirements of Controlled Substances Act
- Comply with laws and regulations within practicing state
- Responsible opioid prescribing
- Schedules II, IIN, III, IIIN, IV, & V
- Registered activity within schedule is restricted by individual state
- Restrictions MI: Physician delegation WN hospital setting, hospice or free standing surgical out pt facilities only, allows Schedule II-seven day supply. Schedules III-V allowed.

source: [www.michigan.gov/healthlicense](http://www.michigan.gov/healthlicense)

link: health profession license

# Responsible Opioid Prescribing

- Evaluation of the patient, including risk assessment
- Development of a treatment plan
- Informed consent and agreement for treatment

## Opioid Contract

- Periodic review
- Consultation
- Maintenance of comprehensive medical records
- Compliance with controlled substances laws and regulations

# Outcomes regularly assessed and documented

- The 4 As:

**A**nalgesia

**A**ctivities of daily living

**A**dverse effects

**A**berrant behaviors

Passik

# Michigan Automated

## Prescription System (MAPS)

- Replaces Official Prescription Program effective 1/1/03.
- Requires electronic reporting of all controlled substances in Schedules II thru V by pharmacies.
- Serialized (OPP) forms not required.
- Schedule II scripts valid for 60 days
- Multiple Schedule II prescriptions per script
- <https://sso.state.mi.us/>;  
[www.michigan.gov/mimapsinfo](http://www.michigan.gov/mimapsinfo)

# Schedule III

- Requires prescription; moderate abuse potential; max 5 refills/6 month period
- Verbal orders allowed
- Examples: anabolic steroids, dronabinol, ketamine, opioids (some combos)
- Vicodin

# Schedule IV (C-IV)

- Less abuse potential than C-III with minimal liability for dependence
- Outpatient Rx can be refilled 6 times within 6 months from date of issue
- Telephone orders acceptable

alprazolam butorphanol

chloral hydrate

codeine (elixir)

diazepam

diphenoxin/atropine

lorazepam

pentazocine

propoxyphene

sibutramine zaleplon

zolpidem

# Schedule V (C-V)

- Minimal potential for abuse
- Number of refills determined by prescriber
- Some products (cough suppressants, antidiarrheals) may be available without a prescription

buprenorphine

diphenoxylate/atropine

# Risk Evaluation & Mitigation Strategies

# What is a REMS?

- Strategies for managing a known or potential serious risk associated with a drug or biological product
- Required if FDA deems it necessary to ensure product's benefits outweigh its risks
- May be required by FDA before or after a product has been approved for marketing
  - If FDA becomes aware of new safety information after original approval, agency can require a REMS

# The FDA Amendments Act of 2007

- REMS approved for more than 150 drugs since 2010; nine of these opioid agents
- FDA now considering the development of classwide REMS for long-acting and extended-release opioids

# History of Opioid REMS

- Under FDA Amendment Act 2007, authority granted to FDA to require REMS as part of drug approval application
- February 2009, FDA notifies opioid manufacturers REMS will be required on long acting and extended release opioids
- July and August 2009, two new drugs approved with REMS: Onsolis (IR) and Embeda (ER)
- 5/2011, FDA and industry meet, discussion on next step for REMS implementation through a single system

**The FDA's Rationale  
for a Classwide REMS  
on Controlled-Release  
Opioids**

# Why is a Classwide REMS necessary?

- According to the FDA:
  - Prescription opioids “are at the center of a major public health crisis of addiction, misuse, abuse, overdose and death.”
  - The scope of the problem with prescription opioids has grown since 2000 and continues to worsen
  - Strategies used thus far have not adequately addressed prescription opioid misuse and abuse
  - “The risks must be addressed.”

Source: REMS for Opioid Analgesics: How Did We Get Here? Where are We Going?  
Presented by Bob A. Rappaport, M.D.,  
Director, CDER, FDA on March 3, 2009

# Increase in Opioid Prescribing

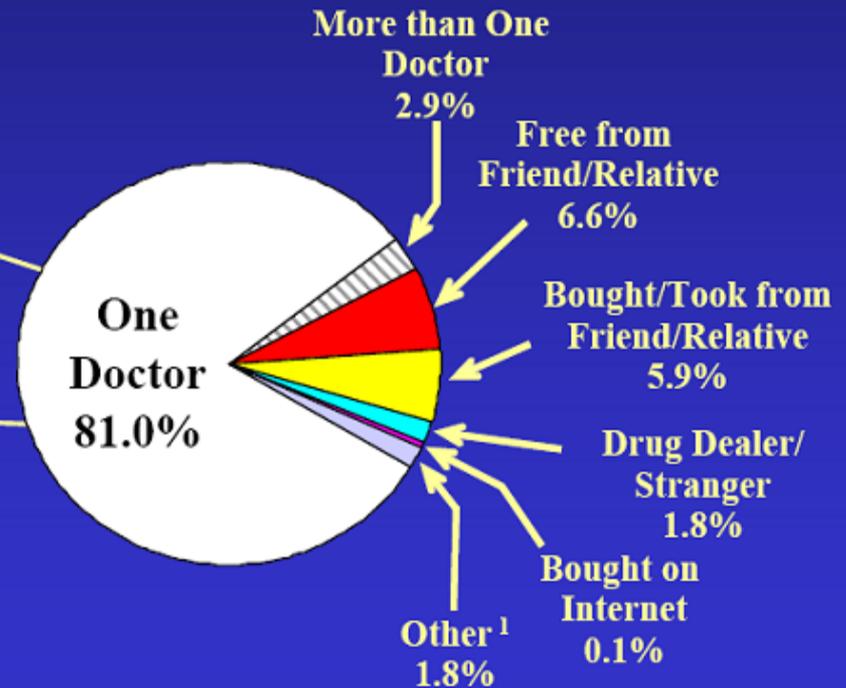
- National Institute on Drug Abuse reports number of opiate prescriptions escalated from about 40 million in 1991 to 180 million in 2007
- 350% increase of opioid prescriptions, at a time when nation's population increased by 19%

# Source of Pain Relievers for Most Recent Nonmedical Use, Past Year Users Aged 12 or Older: 2007

Source Where Respondent Obtained



Source Where Friend/Relative Obtained

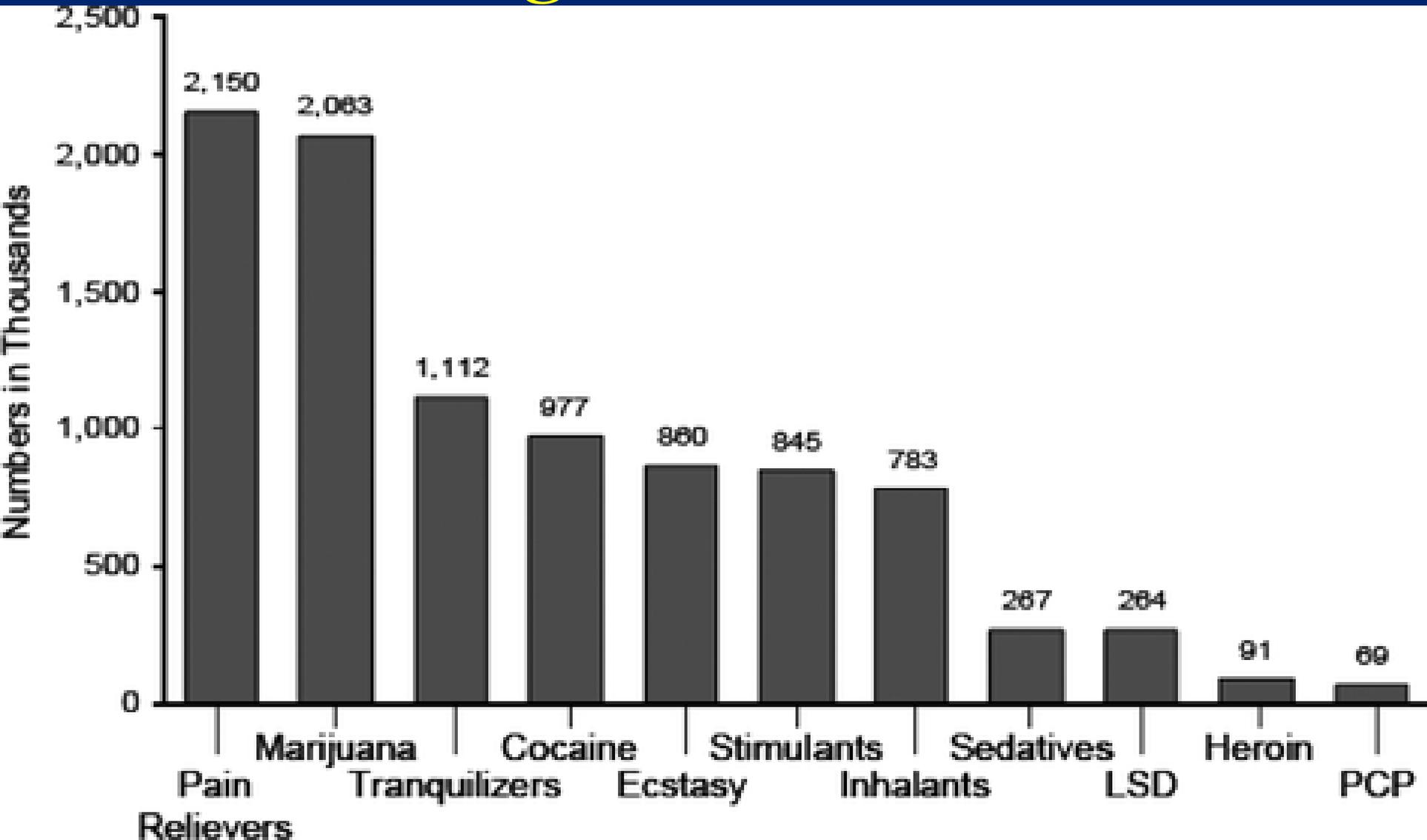


<sup>1</sup> Other category includes: "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/ Pharmacy," and "Some Other Way."

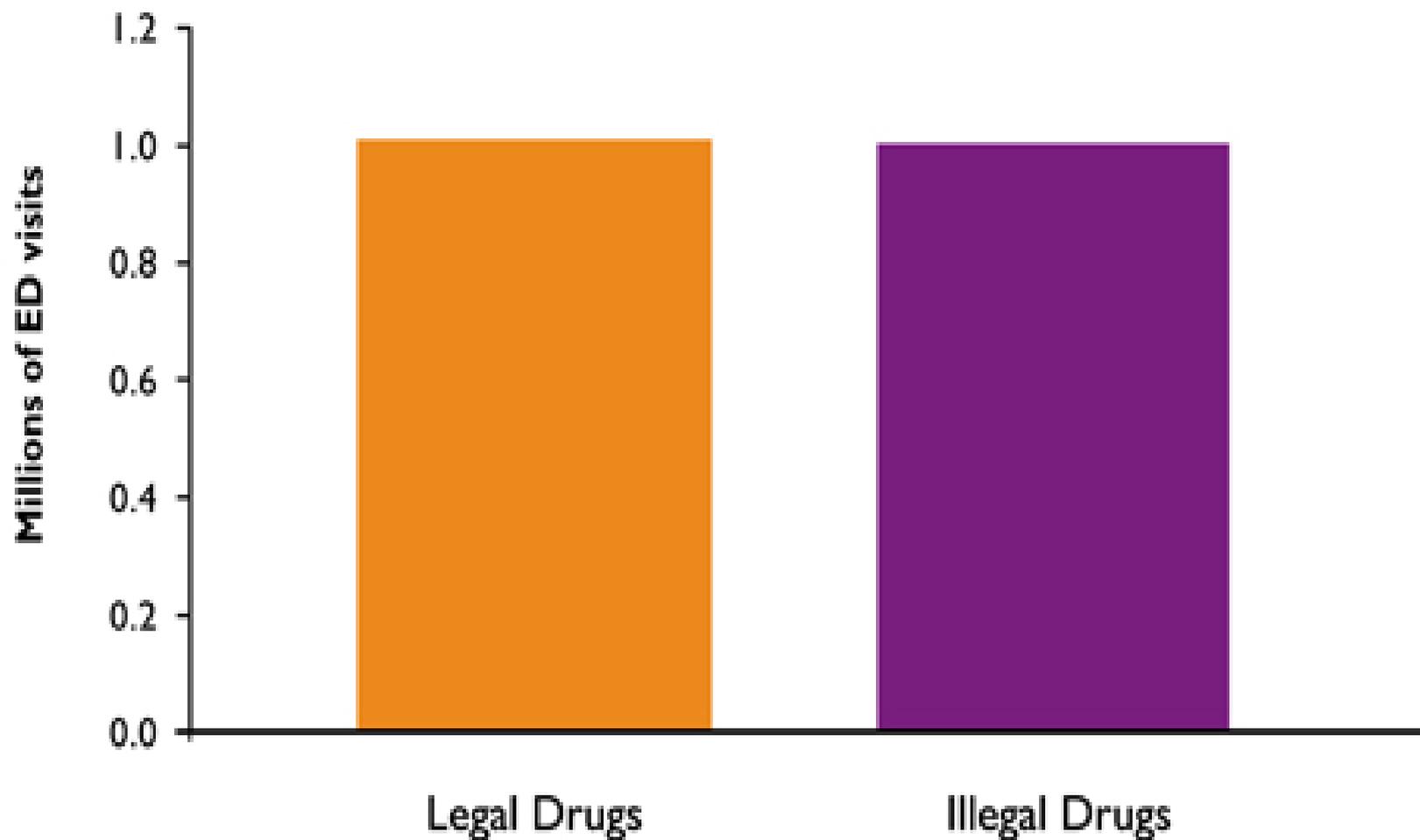
"Note: Totals sum to <100% due to rounding and suppressed estimates."



# Initiates of Specific Illicit Drugs among Persons Aged 12 or Older: 2009

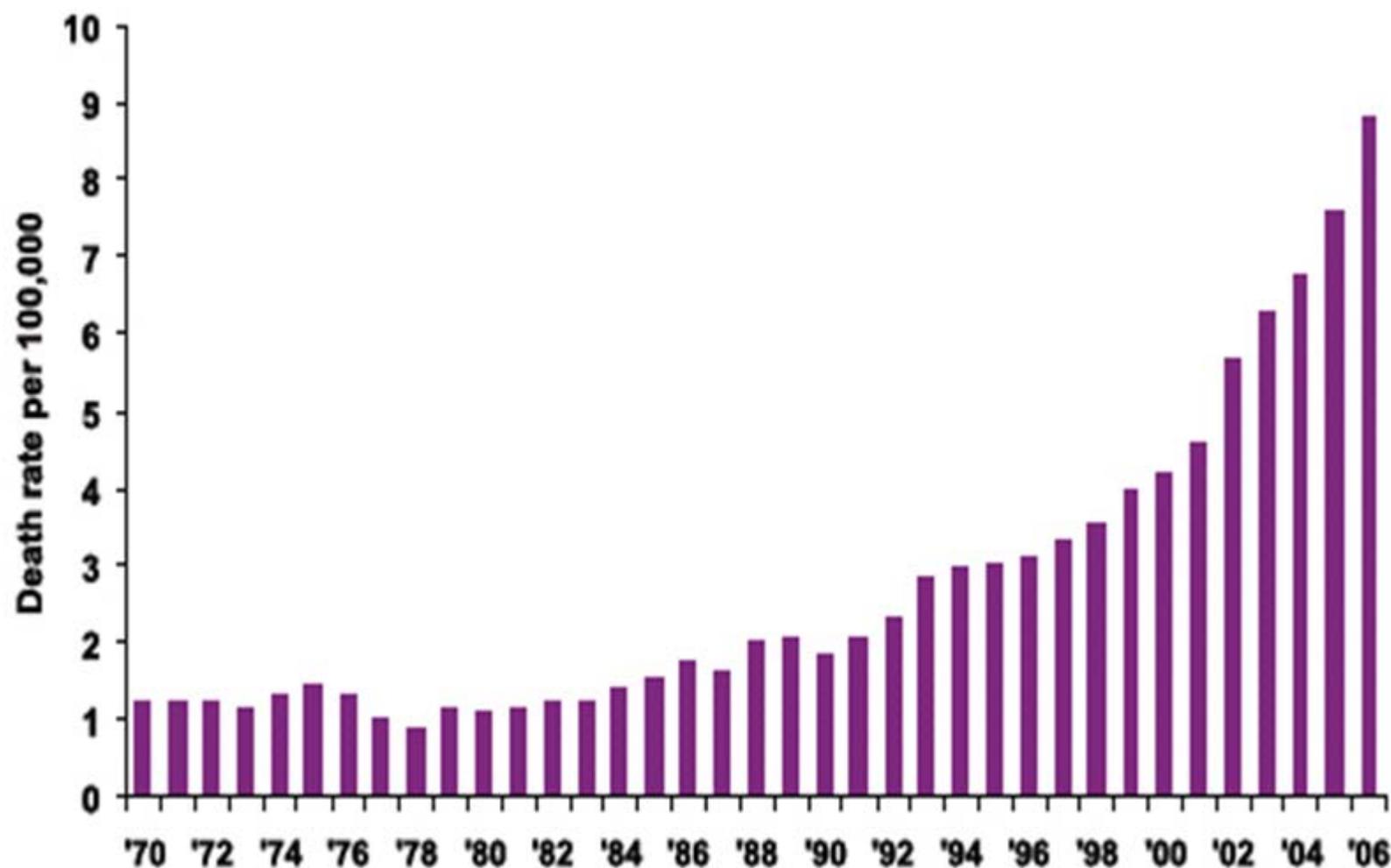


**Figure 5: Estimated numbers of ED visits involving legal drugs used nonmedically and illegal drugs, United States, 2008**



Source: Drug Abuse Warning Network

**Figure 1: Rate of unintentional drug overdose death in the United States, 1970-2006**



Source: National Vital Statistics System

# What are the Goals of the REMS?

- Ensure the benefits of the drugs outweigh the risks
- Ensure health care providers, dispensers, and patients are aware of and understand the risks, as well as the appropriate use, of controlled-release opioids
- Maintain access to prescription opioids for legitimate patients
- Reduce prescription opioid misuse, abuse, addiction, and overdose deaths

# Elements that may be included in a REMS

- Medication Guide (MedGuide)
- Patient Package Insert
- Communication Plan
- Elements to Assure Safe Use (ETASU)
- Implementation System
- Special Labeling Requirements
- Post-approval Studies
- A timetable for assessment of the REMS must be included

# Levels of REMS Restrictions

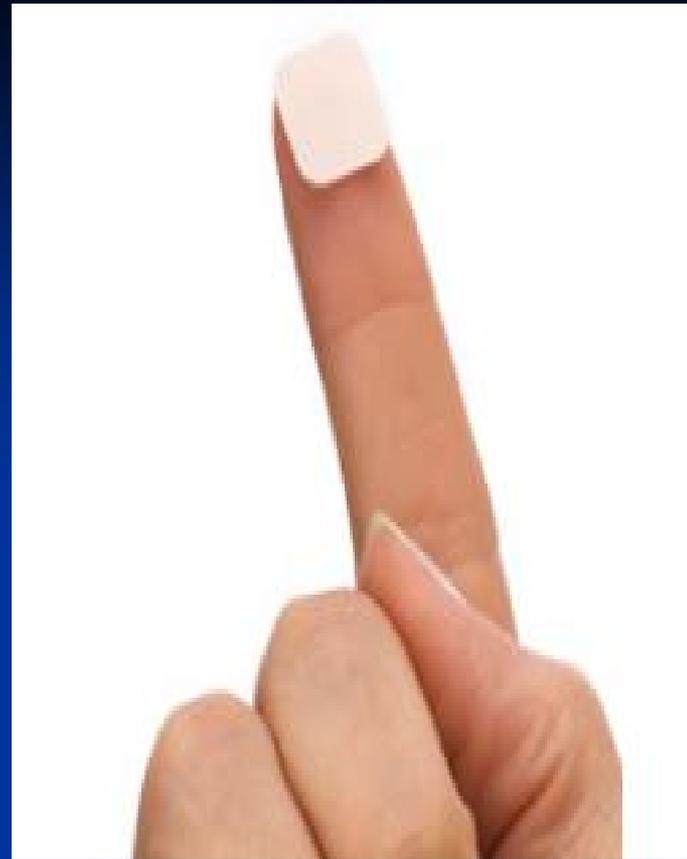


# Onsolis™

fentanyl buccal soluble film®



BEMA Film Placement



**Because fentanyl is subject to abuse and misuse, Onsolis was approved with a Risk Evaluation and Mitigation Strategy, or REMS, which is a required plan for managing risks associated with a drug or biological product.**

# Onsolis-REMS

- National Registry of Prescribers
- Prescriber Training
- Pre-prescribing Exam
- Specializing Pharmacy Distribution Only
- Central screening done by company
  - Double check patient's eligibility
- Insurance clearance
- Delivery to patient's home
- No inpatient distribution

# FDA taking aim at Fentanyl

- Abstral – sublingual tablet
- Actiq – lozenge
- Fentora – buccal tablet
- Lazanda – nasal spray
- Onsolis

# Abuse-Resistant & Deterrent Technologies

- *For many Americans, drug abuse is a painful fact of life. And pain is often the cause. By one estimate, more than 33 million Americans have abused prescription pain killers.*

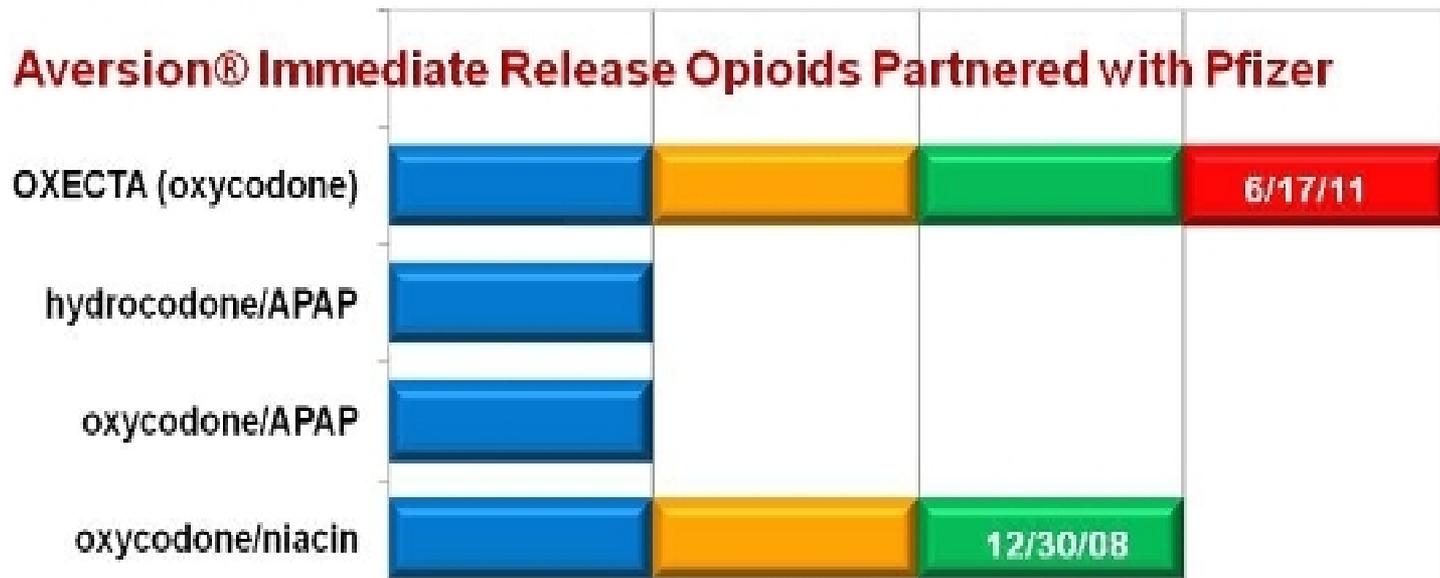
# Pharmaceutical Efforts

- Active ingredient into a matrix; it cannot easily be extracted or that is not easily grounded into powder
- Opioid antagonist is sequestered in inner core of tablet; designed to be released if tablet is crushed or dissolved
- Addition of irritant sequestered into inner core of tablet; designed to be released if the tablet is crushed or dissolved

# Oxecta (Oxycodone IR)

- Polyethylene oxide insoluble to alcohols
- Upon contact with water it forms a viscous gel
- Contains nasal irritant
- Cannot be crushed
- Attempts to dissolve with liquid becomes gummy substance, cannot be injected or snorted

**Aversion® Immediate Release Opioids Partnered with Pfizer**




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**Impede™ Pseudoephedrine (PSE) Tablets**



# Embeda

- Block reward/induce aversive effects if crushed or dissolved
- FDA APPROVES EMBEDA™ FOR MANAGEMENT OF MODERATE TO SEVERE CHRONIC PAIN
- BRISTOL, Tenn., August 13, 2009 /PRNewswire/ — King Pharmaceuticals®<sup>®</sup>, Inc. (NYSE:KG) today announced that the U.S. Food and Drug Administration (FDA) has approved EMBEDA™ (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules for oral use. EMBEDA™ is the first FDA-approved long-acting opioid that is designed to reduce drug liking and euphoria when tampered with by crushing or chewing.

# Embeda



20 mg/0.8 mg



30 mg/1.2 mg



50 mg/2 mg



60 mg/2.4 mg



80 mg/3.2 mg



100 mg/4 mg

# Elite Pharmaceuticals

- Elite is preparing to commence Phase III clinical trials for ELI-216, the only once daily oxycodone containing naltrexone (an opioid antagonist) which provides a superior barrier to abuse compared to the other oxycodone formulations."

# Remoxy

## Physical Abuse resistance, Remoxy™

REMOXY, an investigational drug, is a unique, long-acting oxycodone formulation for moderate-to-severe chronic pain designed to reduce potential risks of unintended use. In mid-2008, an NDA for REMOXY was accepted by the FDA and was granted Priority Review. In December 2008, Pain Therapeutics received a Complete Response Letter from the FDA. Subsequent to the receipt of the Complete Response Letter, King assumed full control of all activities related to the development of REMOXY(r).

To be resubmitted in 2011.



# New River Pharmaceuticals

- **NRP-290**
- **Lysine modified opioid prodrug**
- **Requires biotransformation step to become active**
- **Limited to the GI tract**

# What does the future hold?

- Link DEA certification with mandatory education, would require legislative action
- Implementation of National Prescription Monitoring Program
- Initial REMS education will be implemented in early 2012

ASPMN Task Force  
on REMS

The bottom line is ??????????

**Thank you very much!**

**Questions????**