Risk Evaluation & Mitigation Strategies: REMS

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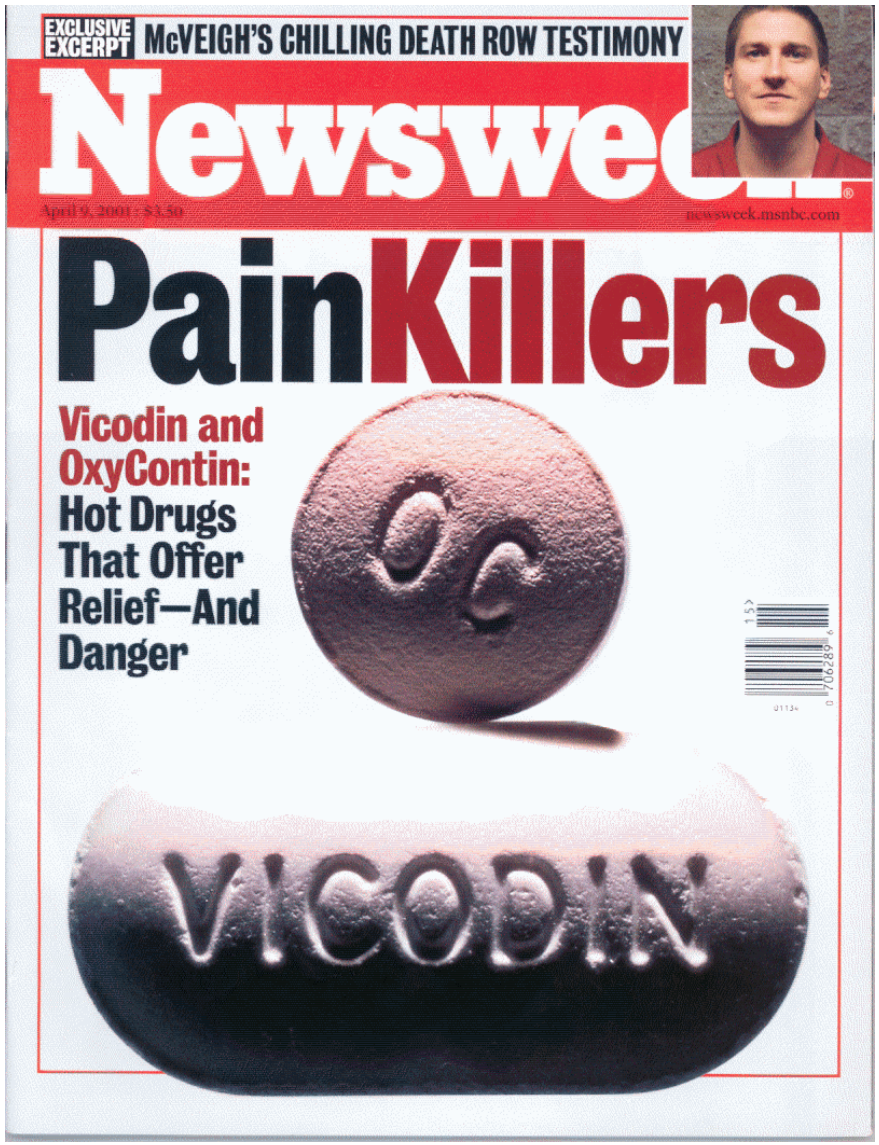
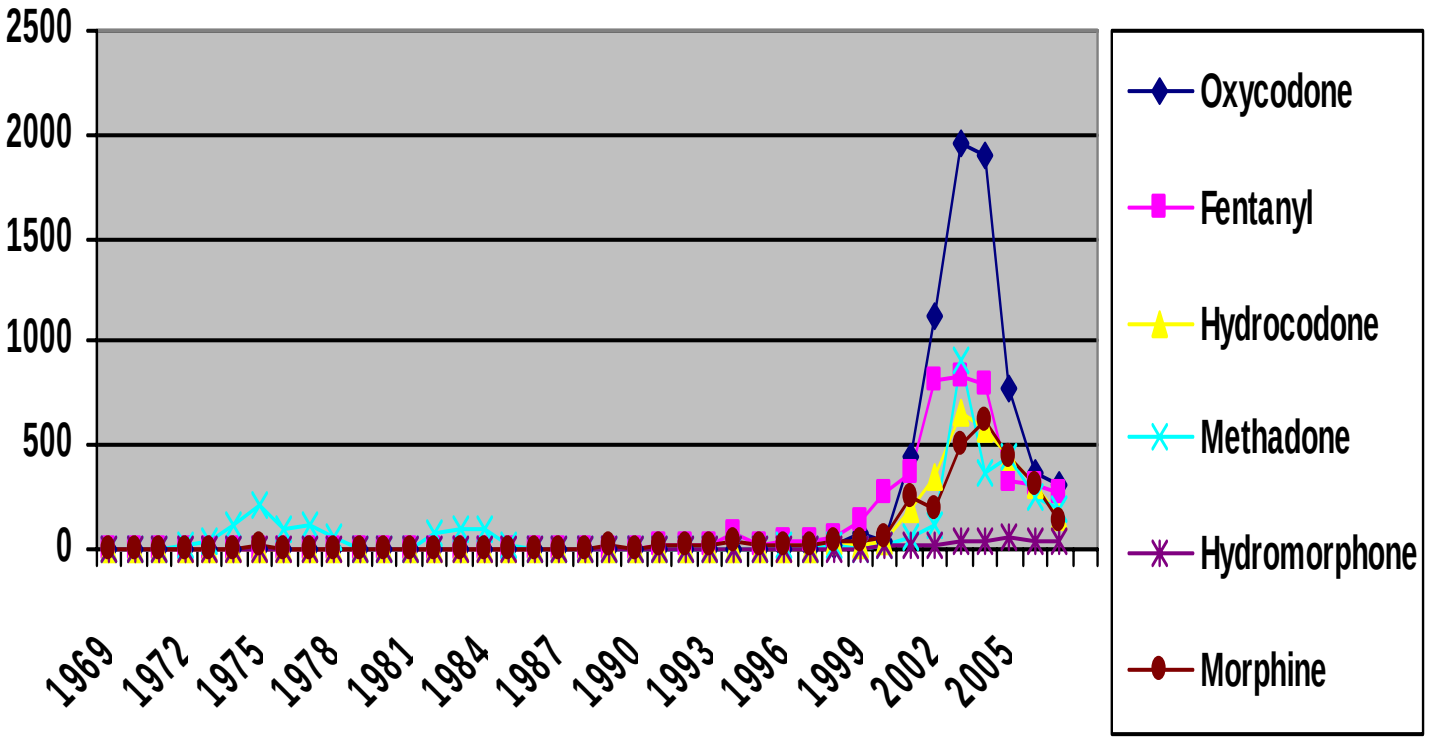
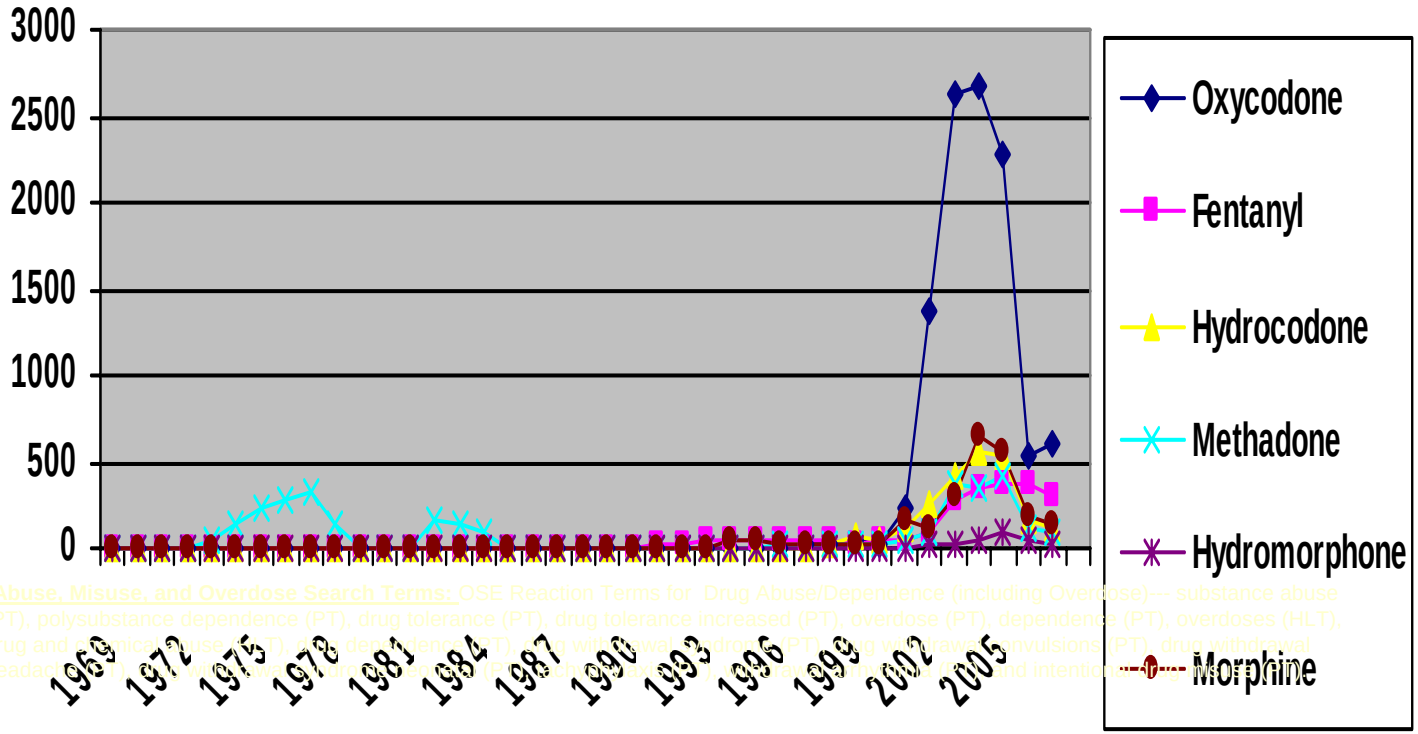
The content of this talk does not necessarily reflect the views of the FDA, and is entirely based on my own observations and viewpoints.


EXCLUSIVE EXCERPT
McVEIGH'S CHILLING DEATH ROW TESTIMONY
Newsweek
April 9, 2001 • $3.50
newsweek.msnbc.com
PainKillers
Vicodin and OxyContin: Hot Drugs That Offer Relief—And Danger
VICODIN

AERS Crude Data of Opioid Products: All U.S. Deaths (1969-1/11/08)



AERS Crude Data of Opioid Products: All U.S. *Abuse/Dependence/OD Reports (1969-1/11/08)



*Abuse, Misuse, and Overdose Search Terms: OSE Reaction Terms for Drug Abuse/Dependence (including Overdose)--- substance abuse (PT), polysubstance dependence (PT), drug tolerance (PT), drug tolerance increased (PT), overdose (PT), dependence (PT), overdoses (HLT), drug and chemical abuse (HLT), drug dependence (PT), drug withdrawal syndrome (PT), drug withdrawal convulsions (PT), drug withdrawal headache (PT), [illegible] and intentional drug misuse (HLT).

Prescription drugs find place in teen culture

By Donna Leinwand, USA TODAY

Updated 6/13/2006 7:40 PM ET

Eddie Cappiello holds his 6-week-old daughter Feb. 7. He died 10 days later after overdosing on a mix of pharmaceuticals.

Managing the Risk

- The Agency has worked with sponsors over the past decade to implement risk management programs for a number of the opioid products.
- However, numerous data sources have demonstrated that these programs have not adequately managed the risks of misuse, abuse, addiction and overdose.
- With the new authorities granted to FDA under FDAAA, we will now be implementing Risk Evaluation and Mitigation Strategies (REMS) for a number of these products

Finding a Balance

- Prescription opioids are at the center of a major public health crisis of addiction, misuse, abuse, overdose and death
- The current strategies for intervening with this problem are inadequate
- The risks need to be addressed

Finding a Balance

- Adequate pain control is essential to good medical practice and mandated by various authorities
- Pain patients need access to potent opioid drug products
- Pain is subjective and can't be quantified except by patient report
- Excessive restriction of, for example, distribution, indication or requirements for prescribing could lead to widespread and unacceptable suffering

REMS

- FDAAA (Public Law 110-85) created a new section 505-1 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355-1) that authorizes FDA to require persons submitting certain drug approval applications to submit a proposed REMS as part of the application.

Section 505-1 – Risk Evaluation and Mitigation Strategies (REMS)

- FDA may require REMS:
  - Before approval: if FDA determines REMS is necessary to ensure that the benefits of the drug outweigh the risks
  - Post-approval: If FDA becomes aware of new safety information and determines REMS is necessary to ensure that the benefits of the drug outweigh the risks

Possible REMS Elements

- MedGuides and/or PPIs (505-1(e))
- Communication plan (505-1(e))
- Elements to assure safe use (ETASU) (505-1(f)(3))
- Implementation system if certain elements to assure safe use (505-1(f)(4))
- Timetable for assessment (505-1(d))

Elements to Assure Safe Use

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Implementation Systems

- REMS may include an implementation system related to ETASU in (B) certification of pharmacies and hospitals, (C) dispense only in certain healthcare settings, and (D) safe use conditions
- May require applicant to take reasonable steps to—

  (A) monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and

  (B) work to improve implementation of such elements by such persons.

Timetable for Assessments

- All REMS must include a timetable for submission of assessments of the REMS
- Timetable for assessment must be at least by 18 months, 3 years, and in the 7th year after the REMS is approved

REMS and Generic Drugs

- Generic drugs are only subject to MedGuides or PPIs, and elements to assure safe use
- Generics must use a single shared system with the innovator or obtain a waiver

REMS Are Enforceable

- May not introduce drug into interstate commerce if in violation of provisions
- Drug may be found to be misbranded
- FDA can impose civil penalties for violations of the Act

REMS must not be overly burdensome

Opioid REMS Development

- A list of the drugs to be included was developed
  - Certain opioid drug products including long-acting and extended-release products
  - ER oxycontin, morphine, hydromorphone and oxymorphone; transdermal fentanyl patches; methadone
- A “straw man” REMS was developed that included an array of possible elements
- A letter including the “straw man” was sent to the manufacturers of the products on the list
- The following slides summarize the elements included in the letter

Opioid REMS - Elements to Assure Safe Use

1. A plan to ensure that TRADENAME will only be prescribed by prescribers who are specially certified under 505-1(f)(3)(A) through the certification process described below:
   a. Prescriber training
   b. Prescribers have obtained certification and attestation

Opioid REMS - Elements to Assure Safe Use

1. (a) Prescribers are trained about:
   - proper patient selection
   - appropriate product dosing and administration
   - general opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
   - the risk of addiction from exposure to opioids, including TRADENAME
   - the risks of TRADENAME including XXX

Opioid REMS - Elements to Assure Safe Use

1. (a) continued:
   - the risk of overdose caused by exposure to an essentially immediate-release form of opioid due to chewing, crushing, or dissolving TRADENAME
   - the risk of overdose due to prescribing TRADENAME at doses of XX mg or greater to opioid non-tolerant patients
   - The need to complete the physician-patient agreement form that will be provided by the sponsor (see Section 3(a)(i) below)

Opioid REMS - Elements to Assure Safe Use

1. (b) Prescribers have obtained certification by attesting to the following:
   - I have been trained and understand the risks and benefits of chronic opioid therapy
   - I understand that TRADENAME can be abused...
   - I understand that TRADENAME are indicated for relief of chronic moderate to severe pain requiring continuous, around-the-clock opioid therapy for an extended period of time.
   - I understand that TRADENAME dosages of XX mg and above are for use in opioid-tolerant patients only.

Opioid REMS - Elements to Assure Safe Use

1. (b) continued:
   - I will prescribe TRADENAME after ensuring documentation of safe use conditions described below.
   - I will review the TRADENAME Medication Guide with all patients at the time of initial prescription.
   - I will require all patients to enter into an agreement ... and to acknowledge receipt of these instructions by signing a physician-patient agreement form.

Opioid REMS - Elements to Assure Safe Use

1. continued:
   c. The sponsor will maintain a list of the prescribers who have obtained the certification, and provide the list to those needing to verify that a prescriber has obtained the required certification.
   d. Prescribers will be retrained and recertified periodically, at a specified interval.

Opioid REMS - Elements to Assure Safe Use

2. A plan to ensure that TRADENAME is only dispensed by pharmacies, practitioners, or healthcare settings (e.g., hospitals) who are specially certified under 505-1(f)(3)(B) by requiring that:

Opioid REMS - Elements to Assure Safe Use

2. continued:

a. TRADENAME is dispensed through certified pharmacies, practitioners, or healthcare settings.

- Train their staff, including pharmacists and practitioners, about the REMS procedures and education materials
- Dispense TRADENAME after ensuring documentation of safe use conditions described below

Opioid REMS – Elements to Assure Safe Use

2. continued:

   b. The sponsor will maintain a list of the pharmacies, practitioners, or healthcare settings who have obtained the certification...

   c. Pharmacies, practitioners, or healthcare settings will be retrained and recertified periodically, at a specified interval.

Opioid REMS - Elements to Assure Safe Use

3. A plan to ensure the drug is dispensed to patients with documentation of the following safe use conditions under 505-1(f)(3)(D):

Opioid REMS - Elements to Assure Safe Use

3. a. A prescriber must document that he or she:

- Has obtained, at the time of first prescribing and every 12 months thereafter, a signed physician-patient agreement form provided by the sponsor that documents the following safe use conditions:
  - patients being prescribed the higher doses (i.e., XX mg and above) are opioid tolerant
  - patients require management of moderate to severe pain by continuous around the clock opioid therapy for an extended period of time

Opioid REMS - Elements to Assure Safe Use

3. a. continued:

- patients have been counseled about the risks and benefits and appropriate use of TRADENAME, and about the risk of overdose due to giving TRADENAME to someone for whom it has not been prescribed
- patients have been provided and reviewed the Medication Guide
- patients have been instructed that TRADENAME are not to be crushed, chewed or dissolved because taking chewed, crushed, or dissolved beads leads to rapid release and absorption of a potentially fatal dose of morphine.

Opioid REMS - Elements to Assure Safe Use

3. continued:

b. Pharmacies, practitioners, or healthcare settings that dispense TRADENAME must document that the drug has been dispensed under the following safe use conditions:

- have dispensed TRADENAME based on a valid prescription from a certified prescriber (to be determined from a list maintained by the sponsor)
- have counseled patients on appropriate product use including the need to avoid the use of alcohol or prescription or non-prescription medications containing alcohol
- have provided each patient a Medication Guide with each prescription and instructed the patient to read it

Opioid REMS - Implementation System

The Implementation System must include:

- –A database of all enrolled entities including prescribers, pharmacies, practitioners and healthcare settings.
- –A plan to monitor distribution data and prescription data to ensure that only certified pharmacies, practitioners, and healthcare settings are distributing and dispensing TRADENAME and that only certified prescribers are prescribing TRADENAME.
- –A plan to monitor and conduct audits of certified pharmacies, practitioners, and healthcare settings to ensure these entities are only dispensing TRADENAME after documenting safe use conditions.

Opioid REMS - Timetable for Submission of Assessments

- The proposed REMS must include a timetable for assessment of the REMS that shall be no less frequent than every six months for the first two years and annually thereafter, after the REMS is initially approved. We recommend that you specify the interval that each assessment will cover and the planned date of submission to the FDA of the assessment. We recommend that assessments be submitted within 60 days of the close of the assessment interval.
- Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

Development of the Opioid REMS

- First external event: educational meeting for all stakeholders, March ‘09
- Followed by a meeting with sponsors of the specific opioid products

Development of the Opioid REMS

- Next, four stakeholders meetings, early May ‘09:
  - Patients and patient advocacy groups (including family members of people lost to addiction and/or OD)
  - Prescribers
  - Dispensers (pharmacy groups, etc.)
  - Other (pain educators, insurers, REMS vendors, etc.

Development of the Opioid REMS

- Most recently, public meeting announced in an FR notice held May 27th and 28th
- All interested parties invited to attend and speak
- Over 600 attendees, plus hundreds of others who listened by webcast
- Over 80 speakers

Development of the Opioid REMS

- Many messages
- Some key concerns:
  - Pilot vs immediate action
  - Include all opioids, including immediate-release vs this would overwhelm prescribers and dispensers
  - Absence of adequate metrics to measure outcomes
  - Assurance that any benefit won't be outweighed by negative impacts
  - Continued access essential vs problem is too serious to allow continued access

Development of the Opioid REMS

- One concept for which there was near universal agreement
  - Educating prescribers and patients is essential
- But no agreement on the best way to do that
- Most felt a single REMS was essential
- Many calls to tie education and credentialing to DEA registration

Development of the Opioid REMS

- Next steps:
  - Public docket for last week's meetings closes June 30th
  - After that, review docket and meeting transcripts Followed by these options:
    - Additional stakeholder meetings
    - Continue on going discussions with our federal partners
    - Advisory Committee meeting
    - Issuance of a REMS letter to industry

Development of the Opioid REMS

- Concerns as we proceed
  - Maintaining the balance
  - Measuring the outcomes
  - The risk of doing more harm than good
  - The risk of doing minimal good at an enormous cost to the health care system
  - Allowing the problems to increase unchecked

Acknowledgements:

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