

## The Changing Landscape of Opioid Analgesics: An FDA Perspective

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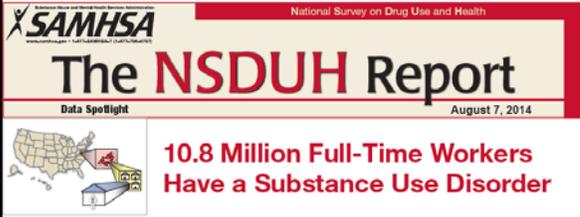
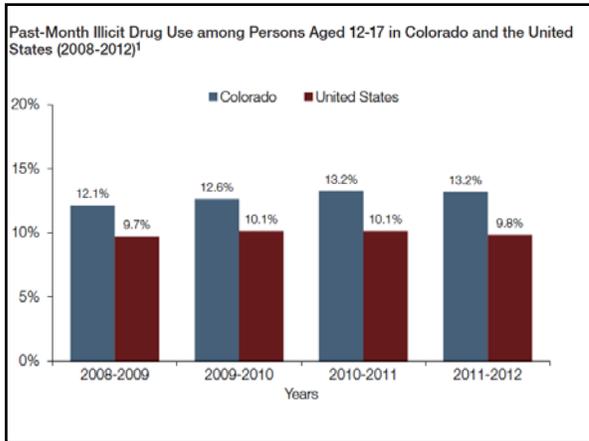
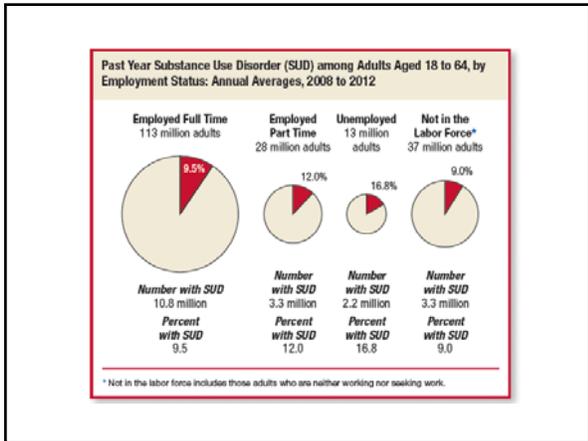


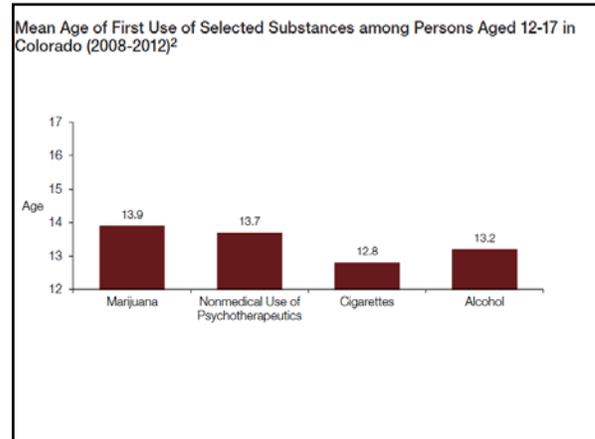
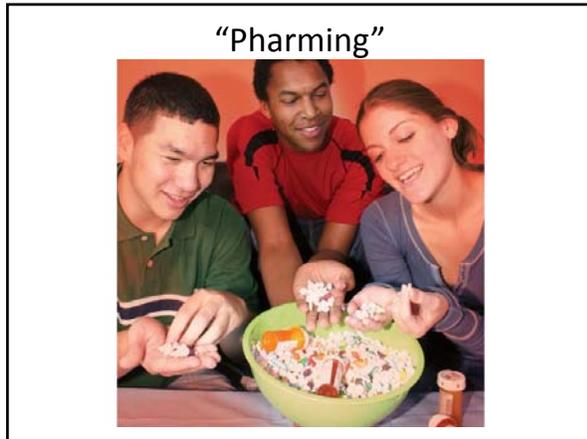

## Disclosures

- Purdue Pharma
- Teva
- Novartis
- CPC Clinical Research
- Claro Scientific LLC

## Objectives

1. Understand the need for new formulations of opioids.
2. Develop an understanding of new opioid anti-abuse technologies.
3. Understand what REMS are and why they are needed.
4. Understand the rationale for naloxone dosing.



**Differentiation**

- **Medical Misuse of Prescription Opioids**
  - Refers to engaging in behaviors not intended by the prescriber such as using too much to get high
- **Non-Medical Use of Prescription Opioids (NMUPO)**
  - Refers to the non-prescribed use of opioids

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  - Refers to the non-prescribed use of opioids
  - 7 out of 10 people who reported lifetime use of opioids intranasally screened positive for past year drug abuse.

Addiction behavior 2007, 32:562-5

**How many drugs are out there?**

- Between 1999 and 2010 opioid sales of opioid analgesics have quadrupled.
- Data on sales shows an increase from 96mg in morphine equivalent/year in 1999 to 710mg year in 2010 per person.
- Between 1997 and 2010
  - Hydrocodone sales increased by 280%
  - Methadone by 1293%
  - Oxycodone by 866%

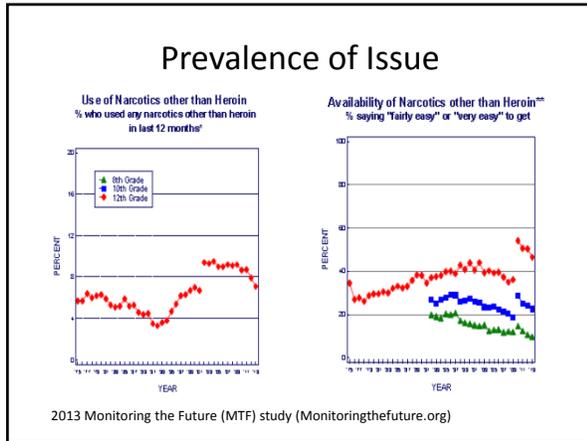
Pain Physician: July Special Issue 2012

**The US and Synthetic Opioids**

- In 2007 the US constitutes 4.6% of the world population.
- In 2007 we consumed 83% of the worlds oxycodone and 99% of the worlds hydrocodone.



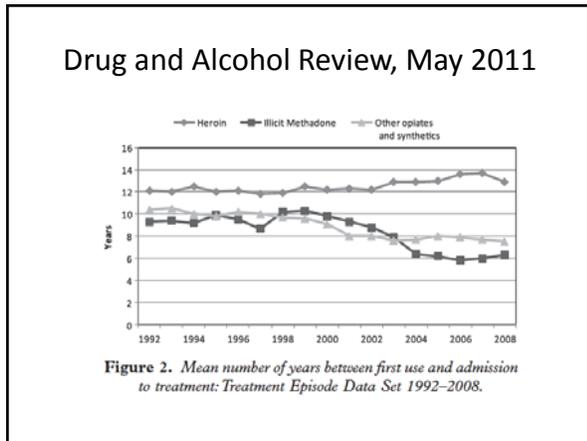




**“Since it is a prescription drug it is safer than illicit drugs”**

	2010	2011	2012	2013
Try any narcotic other than heroin (codeine, Vicodin, OxyContin, Percocet, etc.) once or twice	40.4	39.9	38.4	43.1
Take any narcotic other than heroin occasionally	54.3	54.8	53.8	57.3
Take any narcotic other than heroin regularly	74.9	75.5	73.9	75.8

Monitoring the future report 2013



## A Proactive Response to Prescription Opioid Abuse

Robert Califf et al, NEJM 374:15  
April 14, 2016

Issue	FDA Response
<b>Addressing individual need and societal risk.</b> Patients require access to both and effective pain medication. But both individuals and society must be protected from the effects of opioid misuse.	The FDA will consult with partners including the National Academy of Medicine to create a framework for opioid review, approval, and monitoring that balances individual needs for pain control with the need to protect society from the broader public health consequences of opioid abuse.
<b>Meeting the need for timely action.</b> The evolving threat of opioid abuse requires a flexible, nimble, and iterative approach while the full policy framework is developed.	The FDA Science Board will convene in March to address on the site of other mechanisms for pain management, development of alternative pain medications, and postmarketing surveillance activities. Multiple other actions will address pain management needs for patients, including an evaluation of the existing Risk Evaluation and Mitigation Strategy (REMS) requirements for manufacturers regarding the use of opioids for pain. The FDA will also continue to monitor and address other issues regarding possible expansion of the scope and content of prescriptive education and activities to support the FDA's program to reduce medication misuse, potentially increasing the number of prescribers supporting training in pain management and safe prescribing.
<b>Improving labeling and postmarketing surveillance requirements.</b> Current labeling requirements to include adverse reactions, and manufacturers are required to conduct post-marketing safety surveillance and research studies, but these measures may need to be strengthened.	The FDA will review postmarketing requirements, expanding the requirements that drug sponsors and generic manufacturers must follow when they submit a New Drug Application or Supplemental New Drug Application in the context of opioid and abuse associated with long-term opioid use, including the use of opioids for pain management and other important issues.
<b>Providing clear information on formulation and dosing requirements.</b> Abuse deterrence measures for opioid medications, and broader actions to reduce misuse, may help mitigate harm from opioid overdose.	The FDA will continue to support abuse-deterrence formulations and will continue to work with industry, academia, patient and consumer groups, and other stakeholders to address abuse-deterrence. The FDA will also provide guidance on generic abuse-deterrence opioids and will continue to work to make abuse-deterrence opioids available, including as an over-the-counter medication. In addition, we will continue to work with industry to address other issues.
<b>Addressing the lack of recognized alternatives for pain management.</b> Although recognized alternatives for chronic pain have recently been approved for market, more alternatives are needed, including nonpharmacologic treatments.	The FDA is working closely with industry and the National Institutes of Health to address the needs of the chronic pain population. The FDA is also supporting the ongoing research and development of novel, nonpharmacologic approaches to pain management that have been identified as a top priority.
<b>Creating clear guidelines for opioid use.</b> The current confusion around opioid use and abuse will be resolved, and prescribers will have a clear understanding of appropriate use and management.	The FDA is supporting the CDC's guideline for prescribing opioids for chronic pain. The FDA also supports the ongoing research and development of novel, nonpharmacologic approaches to pain management that have been identified as a top priority.
<b>Managing risks in children.</b> Use of opioid medications in children with severe and chronic pain conditions requires special considerations, and pediatric use of opioids can be particularly risky. The FDA will continue to help these prescribers with medication safety and efficacy, while ensuring access when the benefits outweigh the risks.	An FDA Pediatric Advisory Committee will address the use of opioid medications in children, including the development of high-quality evidence to guide treatment and provide input on the pediatric use of opioids. The Pediatric Advisory Committee will also provide input on the pediatric use of opioids for pain management and other important issues.
<b>Developing a better evidence base.</b> Despite ongoing efforts, the evidence base to guide the use of opioid medications, particularly in the setting of long-term use, is substantially lacking.	Health and Human Services agencies and the FDA program for non-pharmaceutical approaches to pain management are developing a coordinated plan to evaluate the benefits, risks, and costs of pain management and alternative approaches to pain prevention and management.

- ## The FDA will:
- Re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public health effects
  - Convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties;
  - Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved;
  - Develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to the extended-release/long-acting (ER/LA) opioid analgesics labeling that is currently required.
  - Support better pain management options, including alternative treatments.

### The FDA will:

- Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products;
- Update Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements;
- Improve access to naloxone and medication-assisted treatment options for patients with opioid use disorders; and

### Making opioids safer

- “The development of abuse-deterrent opioid analgesics is a public health priority for the FDA,” Douglas Throckmorton, M.D., deputy director for regulatory programs CDER.

FDA news release April 16, 2013

### How Do You Reformulate Opioids to be “Abuse Deterrent”?

### General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Guidance for Industry

Additional copies are available from:  
Office of Communications, Division of Drug Information,  
Center for Drug Evaluation and Research,  
Food and Drug Administration,  
10801 New Hampshire Ave., Bethesda, MD, 4th Floor,  
Silver Spring, MD 20901-0001  
Phone: 855-543-5734 or 301-796-1488; Fax: 301-431-6333  
[druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov) <http://www.fda.gov/Drugs/Guidance/ComplianceandRegulatoryInformation/Guidance/default.htm>

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

November 2017  
Generic

### Routes of Abuse

- Injection: Can you manipulate a pill and make easy to inject?
- Insufflation: (snorting) Can you manipulate a pill and make it easy to insufflate?
- Smoking: Can a pill be inhaled/smoked in either an intact or manipulated form?
- Ingestion: Does manipulating a pill make it more bioavailable when orally taken?

### Approach to Evaluation

- Tier-based approach
- Performance based evaluation of abuse deterrence
- Most effective manipulation
- Sample selection after physical manipulation
- Comparing abuse deterrent formulation to reference product in extraction studies
- Statistical comparison of new to old formulation

## Approaches to Reformulation



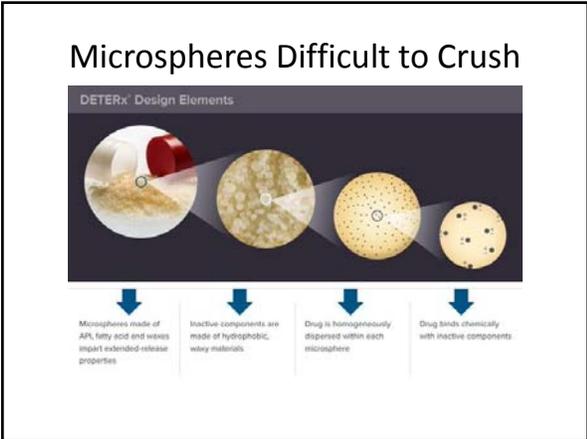
### Big pill difficult to crush

“OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse.”

### Oxycontin Package Insert

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation.

- Increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents.
- When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.



### Microspheres Difficult to Crush

- XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the formulation more difficult to manipulate for misuse and abuse.
- Relative to immediate-release oxycodone tablets, XTAMPZA ER is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents.
- XTAMPZA ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle.

### Oxycodone ER: Reformulated

- “While both original and reformulated OxyContin are subject to abuse and misuse, the FDA has determined that reformulated OxyContin can be expected to make abuse by injection difficult and expected to reduce abuse by snorting compared to original OxyContin.”

Douglas Throckmorton, MD

FDA news release April 16, 2013

### Oxymorphone ER (Opana)

“...Increased ability of the reformulated version of Opana ER to resist crushing relative to the original formulation.

...Reformulated Opana ER can be readily prepared for injection, despite Endo’s claim that these tablets have “resistance to aqueous extraction (i.e., poor syringeability).” It also appears that reformulated Opana ER can be prepared for snorting using commonly available tools and methods.”

FDA statement May 10, 2013

### Roxybond

RoxyBond is the first and only FDA-approved immediate-release opioid medication with abuse-deterrent claims in its approved labeling language

SentryBond™ ....is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse, even if subjected to physical manipulation and/or chemical extraction.

### Other Crush resistant formulations

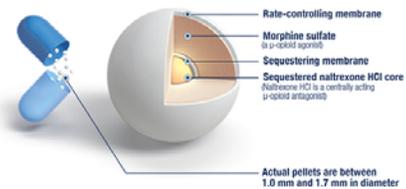
- Morphabond ER (Morphine)
- Arymo ER (Morphine)
- Vantrela ER (12 hour Hydrocodone)
- Hysingla ER (24 hour Hydrocodone)

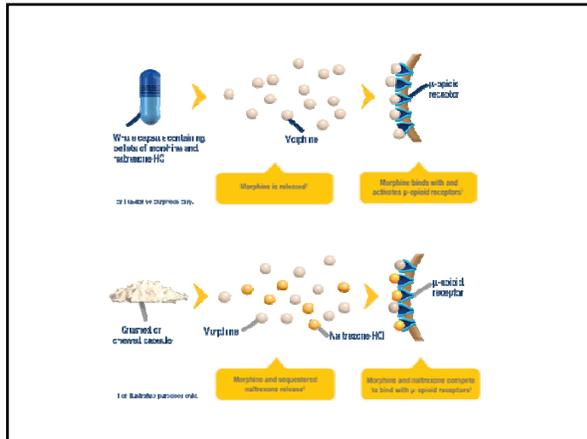
<https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm>

### Combining an Opioid and Antagonist

### Morphine/naltrexone (Embeda)

- Embda approved on November 4, 2013





### Other products?

- Troxyca ER (Oxycodone/Naltrexone) and Targiniq (Oxycodone/Naloxone) have both been discontinued for now.

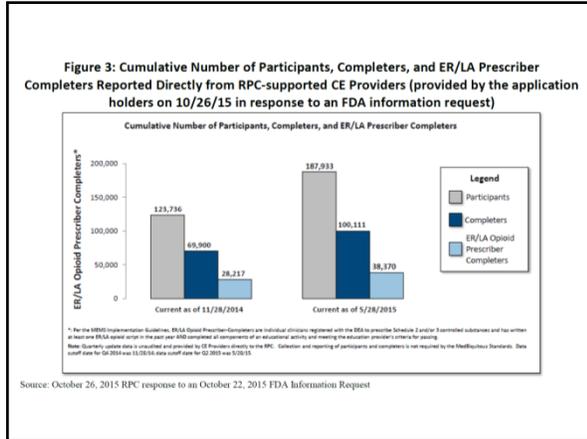
### Other products?

- KemPharm tried to re-engineer hydrocodone to impart abuse-deterrent properties at a molecular level.
- Benzhydrocodone: Bonded hydrocodone to benzoic acid, a widely used food preservative.
- Benzhydrocodone was not pharmacologically active, but had to be metabolized into hydrocodone by enzymes in the intestinal tract to deliver its pharmacologic effects.

FDA website

**FDA Briefing Document**  
 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)  
 May 3-4, 2016

**Extended-release and Long-acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)**



### FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (January 2018)

## Opioid REMS

- To include both ER/LA products and IR products
- Intended to support other national efforts underway to address the misuse and abuse of prescription opioid analgesics

As part of the Opioid Analgesic REMS, all opioid analgesic companies must provide the following:

- Education for healthcare providers (HCPs) who participate in the treatment and monitoring of pain.
  - Education will be offered through accredited continuing education (CE) activities via unrestricted educational grants from opioid analgesic companies.
- Information for HCPs to use when counseling patients about the risks of ER, LA, and IR opioid analgesic use.

## Too Tall a Task?

- The fundamental concepts of pain management, including definitions and mechanisms of pain
- How to assess patients in pain, identifying risk factors for abuse and addiction
- The range of therapeutic options for managing pain, including nonpharmacologic approaches and pharmacologic (non-opioid and opioid analgesics) therapies
- How to integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient
- How to safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings, including initiating therapy, titrating, and discontinuing use of opioid analgesics
- How to counsel patients and caregivers about the safe use of opioid analgesics, including proper storage and disposal
- How to counsel patients and caregivers about the use of naloxone for opioid overdose
- When referral to a pain specialist is appropriate
- The fundamental elements of addiction medicine
- How to identify and manage patients with opioid use disorder

## Result of REMS Trial

- Respondents were knowledgeable about management and counseling requirements for patients being considered for treatment or currently being treated with ER/LA opioid analgesics.
- Respondents were less knowledgeable about assessment of patients, initiation and modification of treatment, and general and product specific information for ER/LA opioid analgesics.
- Since participating in a REMS-compliant activity, respondents reported more often conducting appropriate prescriber behaviors

## Result of REMS Trial

- Half of respondents reported no changes in opioid prescribing behaviors since participating in the CE activity.
- 22% reported writing prescriptions for ER/LA opioid analgesics less often.
- 19% reported writing more ER/LA opioid analgesics prescriptions.
- 38% of respondents reported prescribing more non-opioid medications.
- 23% reported limiting which ER/LA opioid analgesics they prescribe.
- 32% of respondents reported no changes in the types of medications prescribed.



### Clinical and Regulatory Perspectives on Naloxone Products Intended for Use in the Community

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee  
October 5, 2016

Jennifer Nadel, MD  
Medical Officer  
FDA/CDER/OND

Division of Anesthesia, Analgesia, and Addiction Products

## Inside the FDA meeting

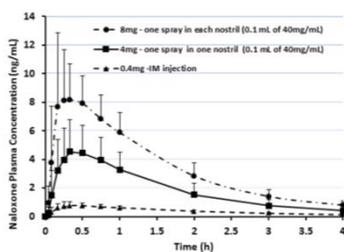
- New concerns over high potency illicit opioids requiring higher doses of naloxone
- We now have companies approaching us about different dosing regimens for these products
- FDA is seeking advice on how to approach these new questions
  - Is our minimum standard high enough?
  - Is there a place for products of different doses/strengths?
  - How would we label a product so a prescriber would know which to choose?

FDA Website

## Regulatory Path Forward

- Infeasible to study minimal effective dose, or conduct efficacy trial
  - Life-threatening nature of opioid overdose
  - Ethical and logistical issue
- Reliance on Agency's previous findings for approved Naloxone Injection
- To establish a scientific bridge via relative bioavailability study between new product and the reference

## Concentration-time Profiles



- Similar  $T_{max}$
- Higher  $C_{max}$  and AUC (~5-fold) for 4 mg Nasal Spray

www.fda.gov

12

## Questions for the Committee

The current pharmacokinetic standard for the approval of naloxone products for use in the community requires demonstration of comparable or greater naloxone levels compared to a minimum dose of 0.4 mg of approved naloxone injection administered by one of the labeled routes of administration.

- a. If you support a different pharmacokinetic standard, describe the rationale for this approach.
- b. Discuss whether this minimum standard for approval is sufficient to address the management of the variety of opioid overdose situations arising in the community or if there is a role for more than one standard for different anticipated situations.

## Questions for the Committee

Different sponsors have proposed different strength doses for their naloxone products intended for use in the community and some have proposed marketing more than one dose strength. Discuss whether there are factors that support different dosing strengths, and how that can be reflected in labeling to assist clinicians in product selection.

## Questions for the Committee

Both children and adults may be at risk for opioid overdose in the home. The current approach has been to require that naloxone products for community use are appropriate for both adult and pediatric use to minimize the risk of product confusion when treating an overdose in the home. Strictly following the pediatric dosing recommendations from the American Academy of Pediatrics (AAP) would require a minimum dose of 2 mg, higher than the current standard for adult products.

- a. Discuss whether there should be products specifically targeting naloxone dosing for children based on the AAP recommendations.
- b. Discuss whether the standard for approval of naloxone products for use in the community should reflect pediatric dose requirements, and comment on the implications for use of these products in adults.
- c. Discuss whether it is acceptable to have different adult and pediatric products available in the home, and how to weigh the risk for product confusion.

### Results

- High degree of controversy over whether dose increase is necessary
- Overall the committee recommended increasing the standard dose.

### Conclusions

- The FDA does have a plan to combat opioid diversion.
- The plan is limited in scope.
- REMS programs are going to become much more prevalent for all prescribers of opioids.
- We as anesthesiologists will have a duty to educate other providers as experts.