REMS

Overview & Clinical Implications of Proposed FDA REMS for Opioids

Objectives

- **Define REMS and background**
- **Review the basic principles and background of the proposed opioid REMS**
- **Review the intentions of the FDA**
- **Cover the chronology of the proposed opioid REMS**
- **Review the clinical implications of a "class-wide" opioid REMS**
- **Discuss some pre-emptive recommendations for best practices with regard to REMS compliance**

Overview

Synne Wing Venuti, MSW

What are REMS?

- ***Risk Evaluation and Mitigation Strategies***
  - On September 27, 2007, the President signed into law the ***Food and Drug Administration Amendments Act*** of 2007 (***FDAAA***)
  - ***NEW* Authorization for** FDA to require certain drug manufacturers to submit a proposed REMS ***if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug***

The Past

- Before *FDAAA* was enacted, FDA required that a *small number* of drug and biological products have **Risk Minimization Action Plans (RiskMAPs):**
  - A strategic safety program designed to meet specific goals and objectives in ***minimizing known risks*** of a product while preserving its benefits
  - Developed for products that had risks that required additional risk management strategies ***beyond describing the risks and benefits of the product in labeling***

Before RiskMAPs

- **Early Risk Management Plans (RMPs) preceded Risk Minimization Action Plans**
  - **Thalidomide – 1998**
    - **Doctors prescribing and pharmacists dispensing thalidomide are required to participate in a program sponsored by the drug's manufacturer, and patients must also be educated about the drug's effects**
    - **Female patients must be tested for pregnancy before and while taking the drug and must use two forms of birth control if sexually active**
    - **Men taking thalidomide must also practice birth control because it is not known if thalidomide can produce defects in the children they conceive.**
    - **Donating of blood or semen and breast feeding are prohibited while taking the drug.**
  - **Actiq – 1998**
  - **Goal was to manage risks**

Role of RiskMAPs

- **Assessment of risks and benefits, minimization of risks and optimization of benefits**
- **Strategic Safety Program designed to meet specific goals and objectives in minimizing product risks**
- **Uses one or more tools to meet desired health outcome**
- **Goes *beyond* FDA-approved labeling**

RiskMAP Tools

- **Redundant reminders/prompting systems**
- **Patient-MD agreements**
  - Attestation of understanding
- **Pharmacy checking mechanisms** (software/stickers)
- **Special packaging or limited supply**
- **Additional communication**
  - Medication Guides
- **Rely on *voluntary* compliance *Enforceable?***

Intentions of RiskMAPs

- **Address *clearly identified risks***
  - *e.g., avoidance during pregnancy, etc.*
- **Programs focused only most important risks**
- **Interventions appropriate to risk**
- **Balance of public safety and patient need**
- **Attempted to provide for readjustments based on data-driven demonstrated success or failure**

The Present

- **NOW** that FDAAA has given FDA the authority to require REMS when necessary to ensure that the benefits of a drug outweigh the risks, FDA anticipates that:
  - A product that would previously have been approved with a RiskMAP will, instead if deemed to be appropriate by the FDA, be approved with a REMS
- ***REMS ARE ENFORCEABLE***
  - Manufacturer's will pay if they are not followed
  - **It all ends up at the doorstep of healthcare providers and patients**

REMS Goals

- **The desired safety-related health outcome *or* the understanding by patients and/or healthcare providers of the serious risk(s) associated with a certain medication**
  - Stated in a way to achieve maximum risk reduction
- **Examples:**
  - Healthcare providers are aware of **how to assess patients appropriately** to determine the risk/benefit ratio
  - **Patients** taking drug "X" **should be aware** of the serious risks relative to potential benefits

Possible REMS Components

- **Healthcare providers should have particular experience or training, or are specially "certified"**
- **For example:**
  - Be able to diagnose the condition for which the product is indicated
  - Understand the risks and benefits of the product
  - Can diagnose and treat potential adverse reactions and negative outcomes associated with that product

Possible REMS Components (Cont'd)

- **Pharmacies, practitioners, *and/or* healthcare settings that dispense the drug should be specially "certified"**
- **For example:**
  - Understand the risks and benefits of the product and have read the educational materials ***before*** the drug is dispensed
  - Fill the prescription only after receiving prior authorization
  - Agree to check labs, or check for presence of criteria indicating that ***the patient*** has met all criteria for receiving the drug
  - Will fill the prescription only within a specified period of time

Possible REMS Components (Cont'd)

- **The drug is dispensed only to *patients* with evidence or other documentation of safe-use conditions**
- **For example:**
  - Patients have been counseled about risks and benefits and signed acknowledgement about them
  - Patients have been provided a copy of patient educational materials **and demonstrated that they understand** the risks and benefits
  - Patients receive the drug only after authorization is obtained **and verified**

Possible REMS Components (Cont'd)

- **Patients are to be monitored or specific follow-up should occur at specified time points**
- **For example:**
  - Lab testing
  - Prescriber contact on a time schedule after beginning treatment
  - Periodic contact with prescriber during *and* following treatment to ensure they did not experience serious risk

Possible REMS Components (Cont'd)

- **A REGISTRY**
  - Access to a drug may be **contingent on patient enrollment**
  - Information gathered may include:
    - Information on clinical outcomes
    - Clinical and laboratory data
    - Safety information
    - Data on compliance with prescribed management and prescribing protocols
    - Data on the impact of tools on ensuring compliance and outcomes

Possible REMS Components (Cont'd)

- **A survey to evaluate knowledge about a serious adverse event to either prevent it or to evaluate use and/or labeling**
- **Additional information may include:**
  - Use be prescriber specialty
  - Patient-level data (age, gender, race, etc.)
  - Length of therapy
  - **Indication for therapy**

Questions?

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Opioids for Chronic Pain

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Opioids, Chronic Pain, and REMS

Kevin L. Zacharoff, MD

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Opioids and Chronic Pain

- **Increasing expectations of pain assessment and compassionate treatment**
  - Joint Commission standards on pain assessment[1]
  - Pain is designated ***the 5th Vital Sign***
- **The Hospice movement towards more humane and improved quality of life in terminal patients**
  - Documented instances of under-treated pain
- **More of these patients may survive and become chronic pain patients, tolerant to opioids**

1. The Joint Commission's 2001 pain management standards state that every patient has a right to have his or her pain assessed and treated. These standards were the product of a two-year collaboration between the Joint Commission and the University of Wisconsin – Madison Medical School.

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Chronic Pain

- **Pain is one of the most common reasons for seeking medical attention**
  - The population is aging, and the % of people with chronic pain increases in almost a linear fashion
  - New conditions are being identified – i.e., fibromyalgia
  - Poorly controlled acute pain may be more likely to develop into chronic pain
- **Economic consequences**
  - Productivity
  - Absenteeism
  - Billions in healthcare $$

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Opioids and Chronic Pain

- **Opioids have demonstrated to be effective in treating chronic pain in a variety of clinical conditions**
- **Alternatives to opioids carry risk**
  - NSAIDS
  - COX-2s
  - Surgery
- **Can be safely and effectively if used appropriately…**
  - By prescribers
  - By patients

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Challenges to Healthcare Providers

- **To name *a few*:**
  - Policies – **Assess and treat**
  - Guidelines – **APS/AAPM, Joint Commission, AAHPM, ACS**
  - Expectations – **Treat or be sued, bill of rights**
  - Ever-shorter office visits – **7 minutes or less?**
  - Complicated patients – **Hx of addiction or abuse**
  - Little training in pain management and aberrant drug-related behavior – **Educational deficits are huge**
  - Regulatory scrutiny – **FDA, DEA, FDAAA, etc.**

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Opioid Risk

- ***Old definition***
  - The potential for opioid analgesia adverse effects
    - Constipation
    - Nausea/Vomiting
    - Dry mouth
    - Itching
    - Sweating
    - **Respiratory Depression**

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Opioid Risk

- ***New definition***
  - Adverse effects
  - Aberrant drug-related behavior
    - Abuse
    - Misuse
    - Diversion
    - **Addiction**

—**Unintended Deaths**

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Opioid Prescribing on the Rise

- **Extended-release and long-acting opioids**
  - Outpatient retail pharmacies accounted for approximately 76%[1] of distribution in 2009
- **Immediate-release opioids**
  - Approximately 60%[1] distributed in retail pharmacies
  - Morphine (single ingredient) and combination codeine products primarily through non-retail pharmacies
- **About 50% of prescriptions are prescribed by primary care practitioners**

1. IMS Health, IMS National Sales Perspectives, Year 2009

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How did RiskMAPs for Opioids Turn Out?

- **The FDA (*and everyone else)* thinks that RiskMAPs did not get the job done**
  - Voluntary nature possibly lacked efficacy
  - Incidence of aberrant drug-related behaviors continues to rise now called "**non-medical use**"
  - Inability to monitor efficacy over time despite intentions with respect to opioid risk

—↑↑ **Unintended deaths** ↑↑

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New Report on Opioid Abuse

- **July 15, 2010[1]**
  - The proportion of all substance abuse treatment admissions ***age 12 or older*** that reported any pain reliever abuse increased more than fourfold between 1998 and 2008, from **2.2 to 9.8 percent**
  - Increases in percentages of admissions reporting pain reliever abuse **cut across age, gender, race/ethnicity, education, employment, and region**
  - Among admissions for which medication-assisted opioid therapy was planned, reports of pain reliever abuse ***more than tripled*** from **6.8 percent in 1998 to 26.5 percent in 2008**

1. The TEDS Report is published periodically by the Office of Applied Studies, Substance Abuse and Mental Health Services Administration (SAMHSA)

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More Bad News

- **In 2008, among the population of the United States *age 12 or older*, non-medical use of prescription pain relievers was the *second most prevalent type of illicit drug use*, after marijuana use**
- **The majority of non-medical users of prescription pain relievers in the past year (*55.9 percent*) obtained their pain relievers most recently from a friend or relative for free, and another 8.9 percent bought them from a friend or relative.[1]**

1. Office of Applied Studies. (2009). *Results from the 2008 National Survey on Drug Use and Health: National findings* (NSDUH Series H-36, HHS Publication No. SMA 09-4434). Rockville, MD: Substance Abuse and Mental Health Services Administration.

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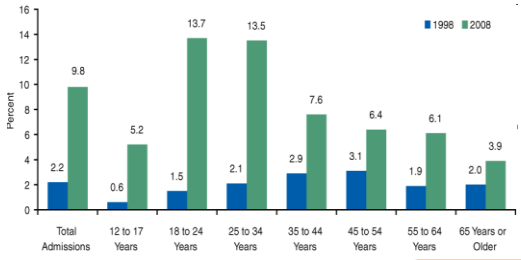
Percentages of Substance Abuse Treatment Admissions within Specific Age Groups That Reported Any Pain Reliever Abuse: 1998 and 2008



Source: SAMHSA Treatment Episode Data Set (TEDS), 1998 and 2008.

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It gets *Worse*

- ***National Survey on Drug Use and Health -2009***
  - In 2008, more than 13% of all Americans age 12 and older have used a prescription pain medication *non-medically* at least once in their lifetime
  - More than 2 million Americans age 12 and older initiate non-medical use of a prescription pain reliever each year; this rate has remained *unchanged* for the past 5 years
  - **Most non-medical users of prescription pain medications obtained it from a *single* healthcare provider or clinical setting**

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Opioid REMS – *Not here yet – but Coming*

- **Prescription opioids continue to be an increasing problem with respect to adverse events & abuse**
- **Prescription opioid abuse contributes to crime & violence**
- **Inadequate patient supervision *following* prescription of opioids, leading to:**
  - Overdose
  - Iatrogenic addiction
  - Continued dosing in patients who no longer need treatment
  - Recreational use (including high school and college students)

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Questions?

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"*The Letter*" about REMS

- **Written to all manufacturers of extended-release/long-acting opioids from the FDA**
  - This letter is to inform you (*insert manufacturer's name*) that the Agency has determined certain opioid products, including *DRUG NAME*, will be required to have Risk Evaluation and Mitigation Strategies (REMS), to ensure that the benefits of the drugs continue to outweigh the risks of:
    - **Use of certain opioid products in non-opioid-tolerant individuals**
    - **Abuse**
    - **Overdose, both accidental and intentional**
  - The REMS will include elements to assure safe use to ensure that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products

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The FDA's Statements

- *"The agency has long been concerned about adverse events associated with this class of drug and has taken steps in cooperation with drug manufacturers to address these risks.* ***We intend to use the agency's REMS authority under the Food and Drug Administration Amendments Act of 2007 (FDAAA) to mitigate the risks of these drugs"***
- *"Opioid drugs have benefit when used properly and are a necessary component of pain management for certain patients"*
- ***"Opioid drugs have serious risks when used improperly"***
- *"Despite these efforts (RiskMAPs), the rates of misuse and abuse, and of accidental overdose of opioids, have risen over the past decade"*

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The REMS Rationale

- *"The FDA believes that establishing a REMS for opioids* ***will reduce these risks, while still ensuring that patients with legitimate need for these drugs will continue to have appropriate access****"*
- ***"The REMS would be intended to ensure that the benefits of these drugs continue to outweigh certain risks"***

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In Summary

- *"The FDA, drug manufacturers, and others have taken a number of steps in the past to prevent misuse, abuse and accidental overdose of these drugs, including providing additional warnings in product labeling, implementing risk management plans (RiskMAPs), conducting inter-agency collaborations, and issuing direct communications to both prescribers and patients. Despite these efforts, the rates of misuse and abuse, and of accidental overdose of opioids, have risen over the past decade.* ***The FDA believes that establishing a REMS for opioids will reduce these risks, while still ensuring that patients with legitimate need for these drugs will continue to have appropriate access".***

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Questions?

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Opioid REMS

What does (or will) it all mean?

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Chronology

- **February 6, 2009 -** FDA sent letters to sponsors
- **March 3, 2009 -** Meeting held between FDA and sponsor industry representatives
- **May 4 and 5, 2009 -** FDA Stakeholder Meetings
  - FDA Docket No. *FDA2009N0143* opened to accept public submissions on the topic from all possible stakeholders
- **May 27 and 28, 2009 -** FDA Public Hearing
- **June 30, 2009 -** FDA Docket No. *FDA2009N0143* closed
- **September 30, 2009 -** Draft Guidance on Format and Content of REMS released for comment
- **October 19, 2009 -** FDA Docket No. *FDA2009N0143* re-opened for one year (scheduled to close October 19, 2010)
- **December 4, 2009 -** FDA Public Hearing

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Stakeholders

- **The Federation of State Medical Boards**
- **Government agencies**
- **Prescribers**
- **Patient and consumer advocates**
- **Pharmacists/dispensers**
- **Pain and addiction treatment communities Professional societies**
- **State Licensing Boards**

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Impact on Stakeholders

- From a clinical perspective this initiative stands to ultimately impact a significant number of stakeholders
- Among them are the approximately 1 million DEA registrants, including the 680,000 active physician (MD or DO) registrants, who write approximately 28 million prescriptions for extended-release opioids, for approximately 4 million patients each year

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"Class-wide" Opioid REMS – Some Important Questions

- ***Is it truly "class-wide"?***
- **Does the higher incidence of non-medical use occur with immediate-release, or extended-release formulations?**
  - Does it matter?
- **Will forcing requirements on prescribing the extended-release meds just push people towards writing for more of the short-acting ones?**
- **Will that possibly worsen the problem?**

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Unintended Consequences

- **Decreased access to these pain medications for legitimate medical purposes**
- **Shifts in prescribing to opioids not covered by the REMS and other pain medications**
- **Healthcare providers "opting out" of pain management due to burdensome certification requirements**
- **Negative impact on the care of disparate groups of chronic pain patients, such as those in rural areas, the poor, ethnic and racial minorities, and women**

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What's happened so far?

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Industry Working Group (IWG)

- **A group independent of the FDA was formed and consisted primarily of the affected medication's sponsors, advocacy and policy groups, and other non FDA stakeholders**
- **Met regularly to provide a forum to work collaboratively with other stakeholders in order to develop a REMS plan that would satisfy the goals of the FDA**
- **These goals needed to include key components of the REMS, *as well as* a mechanism to measure how effectively the REMS would be able to achieve its desired goals over time**

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Docket

- **A docket for public commentary was opened, closed, and then re-opened**
- **Submissions were made by a variety of:**
  - Societies
  - Advocacy groups
  - Healthcare providers
  - Almost everyone who's anyone
- **The FDA welcomed docket submissions on the subject and over 2000 submissions were reviewed and summarized by a team of more than 70 FDA staff members**

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July 22 – 23rd 2010

- **Joint meeting of the FDA's *Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee* was scheduled for July 22 and July 23, 2010**
- **The purpose of this public meeting was to discuss the current status of the REMS initiative, and to "gather additional feedback and comments on FDA's proposal to require a REMS for this class of long-acting and extended-release opioid drug products" along with the draft version developed by the FDA, entitled *Proposed Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids***

Highlights of the Meeting

- **Established Goals**
  - To reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of long-acting and extended-release opioids while maintaining patient access to these medications
    - Adverse outcomes of concern include:
      - Addiction
      - Unintentional overdose
      - **Death**

Highlights of the Meeting

- **The Use of Medication Guides**
  - Specifically to contain language regarding the safe use of all opioid drug products
  - Product-specific information

Elements to ASSURE Safe Use (*ETASU*)

- **Prescriber Education (*Voluntary*)**
  - Information about appropriate patient selection, dosing, and patient monitoring
  - Training for patient counseling on the safe use, storage, and disposal of opioids
  - Demonstration by sponsors of prescriber training, and that the knowledge of appropriate use was improved, via surveys of the prescribing community
  - No formal prescriber enrollment or real time verification of the training at the pharmacy level

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- **Patient Education**
  - Counseling by physicians on risk and safe use
  - Patient Education Sheets
  - No patient registry would be required

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- **Timetable for REMS Assessment of Efficacy**
  - All REMS would be required to contain a timetable for assessment of efficacy
  - Assessments would include
    - The effectiveness of the program in reducing serious adverse outcomes from misuse and abuse
    - The impact on the appropriate access to pain medications

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- **Metrics to Measure REMS Efficacy**
  - To include process measures and measures of patient and prescriber knowledge
  - Tracking certain behaviors (such as non-medical use of prescription opioids)
  - Adverse events (unintentional overdose, addiction, and deaths related to prescription opioids)
  - Access to care

More

- **In addition to requiring sponsors to implement a REMS for the class of long-acting and extended-release opioids, FDA stated that it also intends to partner with other Federal agencies and appropriate stakeholders in the private sector, under the *Agency's Safe Use Initiative***
  - The goal of this partnership would be to implement programs that more broadly address the problem of misuse and abuse of prescription opioids
    - Including appropriate storage
    - Disposal
    - Avoidance of improper sharing for therapeutic use, misuse, or abuse

The Opioid REMS Committee

- **Panel of 35 experts selected to give feedback to the FDA on the proposed REMS**

What they Decided

- **Discussing the problem at hand**
  - There was almost universal consensus that the **"status quo" is not sufficient**, and that prior efforts have not been effective
  - Additionally, there was a strong feeling by some members of the committee that using a REMS that only applied to long-acting and extended-release opioids, might create a ***"balloon effect"***, pushing prescribers towards short-acting opioid formulations
    - Many committee members thought a REMS should be applied to ***all formulations*** of opioids in order to significantly impact the unintended adverse effects

What they Decided

- **Discuss the proposed FDA draft REMS and its potential impact**
  - In addition to the above comments, the committee felt that **a voluntary program of prescriber education would likely be ineffective**, and that it should, to some degree, be a requirement
  - Suggestions were made that about **tying educational fulfillment to DEA registration**
  - Although some members thought that excluding short-acting formulations would be troublesome, they did concede that targeting the long-acting and extended-release formulations would be a good beginning, and that **following initiatives should likely target the entire class of medications**

What they Decided

- **Voted on agreement or disagreements with the FDA's proposed REMS**
  - The committee voted **25-10 *against*** recommending the FDA's proposed draft as it was presented, for a variety of reasons including those listed above

What they Decided

- **Discuss how the FDA could work with sponsors to develop the necessary educational programs**
  - There was little consensus on these programs, other than that they should obtain some sort of approval, take into consideration patient levels of health literacy, and be meaningful in their nature and content
  - For prescribers, a form of continuing medical education might be effective

What they Decided

- **Discuss how to measure the impact of the REMS**
  - There was little agreement about how to measure the impact, although most members of the committee agreed that exploring meaningful sources of data that could provide timely information would be a valuable step

Finally

- **The meeting adjourned with the overall recommendation that more work needs to be done in order to find a more workable and effective solution to what most people consider is a problem approaching a crisis level**
- **Education was resoundingly described as an integral component to a successful REMS, at *both* the provider and patient level**

In Summary

- **There *is* agreement that it is essential to make sure that appropriate candidates for opioid analgesics have appropriate access to these medications, while at the same time trying to balance the risks of abuse, misuse, and unintended deaths**
- **Decisions need to be made about incorporating the best available metrics to measure the impact of REMS, as well as whether this will be a true "class-wide" REMS, covering all opioid medications**

In Summary

- **One thing is for sure – education will be a key ingredient of the ultimate solution**
- **It is a "perfect storm" with respect to chronic pain, opioids, and the non-medical use crisis**
- **Better practices will need to be implemented**
  - **Universal Precautions**
  - **Opioid Risk Assessment**
  - **APS/AAPM Guidelines**
  - **State Guidelines (i.e., Utah)**
  - **Documentation, Documentation, Documentation**

Questions?