Tufts Health Care Institute Program
on Opioid Risk Management *Risk Evaluation and Mitigation Strategy for Prescription Opioids:*

An In-Depth Review of Fundamental Issues

CSS Perspective - Opioid Risk Management

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The opinions and information in this presentation are those of the authors and do not necessarily reflect the views and policies of the FDA

Issues arisen from use of opioids:

- **Opioids present significant risk of overdose, abuse, addiction, and death.**

- **Greater availability of opioids due to increased attention to improving pain management. Most pain patients are treated by primary healthcare providers**
  - **Limited number of pain specialists**
  - **Primary providers may not be well trained in opioid management.**

- **Inadequate patient supervision following prescription of opioids, leading to:**
  - **Overdose**
  - **Iatrogenic addiction**
  - **Continued dosing in patients who no longer need treatment**

- **Prescription opioids have become popular drugs of abuse.**
  - **Addicts**
  - **Recreational users (including high school and college students)**

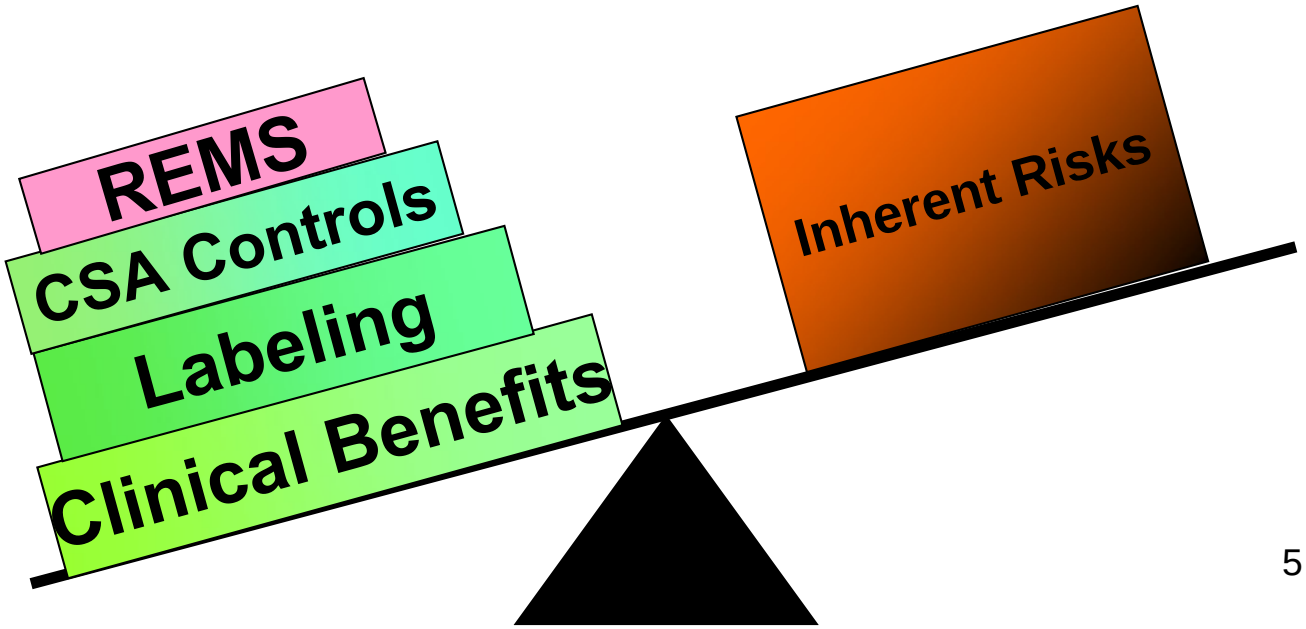
Regulatory Management of the Problem

- ABUSE & DIVERSION
  - Controlled Substances Act (CSA) 1970
  - Purposes
    - to combat drug diversion
    - to assure drug availability for legitimate medical use
    - to comply with international treaties
    - Registration, Prescribing & Dispensing Restrictions, Recordkeeping, Distribution Restrictions, Manufacturing and Import/Export Requirements,

- SAFETY & ABUSE
  - Food & Drug Administration Amendments Act (FDAAA) of 2007
    - Assure safe use
    - Assure access for appropriate patients

FDAAA of 2007

- Ensure that the benefits of the new drug are greater than the risks
- Abuse is part of the safety analysis of the drug



New FDA authorities under FDAAA

- 2007
  - FDA Amendments Act (FDAAA) authorizes FDA to require:
    - Sponsors to develop and comply with Risk Evaluation Mitigation Strategies (REMS)[1]
    - Post-marketing studies and clinical trials[2]
    - Sponsors to make safety-related labeling changes[3]

[1]Section 505-1 of the Federal Food, Drug, and Cosmetic Act
[2]Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act
[3]Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act

Stakeholders Meetings - 2009

- Patient/Patient Advocacy Organizations
- Pharmaceutical Industry & Representatives
- Prescriber Organizations including pain management and addiction treatment communities
  - Physicians, nurses, nurse practitioners, physician assistants) and organizations representing state medical and nursing boards
- Pharmacy Organizations
- Others, including representatives of wholesaler and distributor organizations and hospice care

Public Announcement

- Public Meeting May 27 & 28 2009
  - Asking for input on development of REMS and appropriate use of opioid drug products
  - Seeking practical and effective solutions
- Public Docket
  - Recommendations
  - Advice
  - Comments

July 2009

- Draft Guidance for Industry
  - Postmarketing studies & clinical trials (Section 505(o) of the FFDCA
  - Guidance provides a description of the types of studies and trials that will generally be required
  - FR Notice: Vol. 74, No. 134, July 15, 2009
  - Docket No. FDA-2009-D-0283
  - Comment by October 13, 2009
- Approval of Onsolis with REMS
  - Fentanyl buccal soluble film
  - Available under an approved REMS
    - Intended to reduce the risks
    - Ensure that patients who need the drug to treat pain will continue to have access

Guidance: Postmarketing studies & clinical trials

- Postmarketing commitments (PMCs): Post approval studies to further refine the safety, efficacy or optimal use of a product, or to ensure consistency, and reliability of product quality
- Postmarketing requirements (PMRs)
  - To assess a known serious risk related to the use of the drug
  - To assess signals of serious risk related to the use of the drug; or
  - To identify an unexpected serious risk when available data indicates the potential for a serious risk.

Guidance: PMR Studies under FDAAA

- Pharmacoepidemiology studies
- Clinical trials with a primary safety endpoint
- Safety studies in animals
- In vitro laboratory safety studies
- Pharmacokinetics studies or trials
  - In the labeled population or in a subpopulation at potential risk for high drug exposure
- Evaluation of drug interactions or bioavailability
  - When there are scientific data that indicate a potential for a serious safety risk

Onsolis – New Oral Transmucosal Fentanyl

- FDA's approval of product and REMS is independent of the current effort to develop REMS for extended-release and long-acting opioids
- Onsolis is safe & effective in a much more limited patient population than extended-release and long-acting opioids
  - Not extended-release opioid
  - Only for opioid-tolerant patients

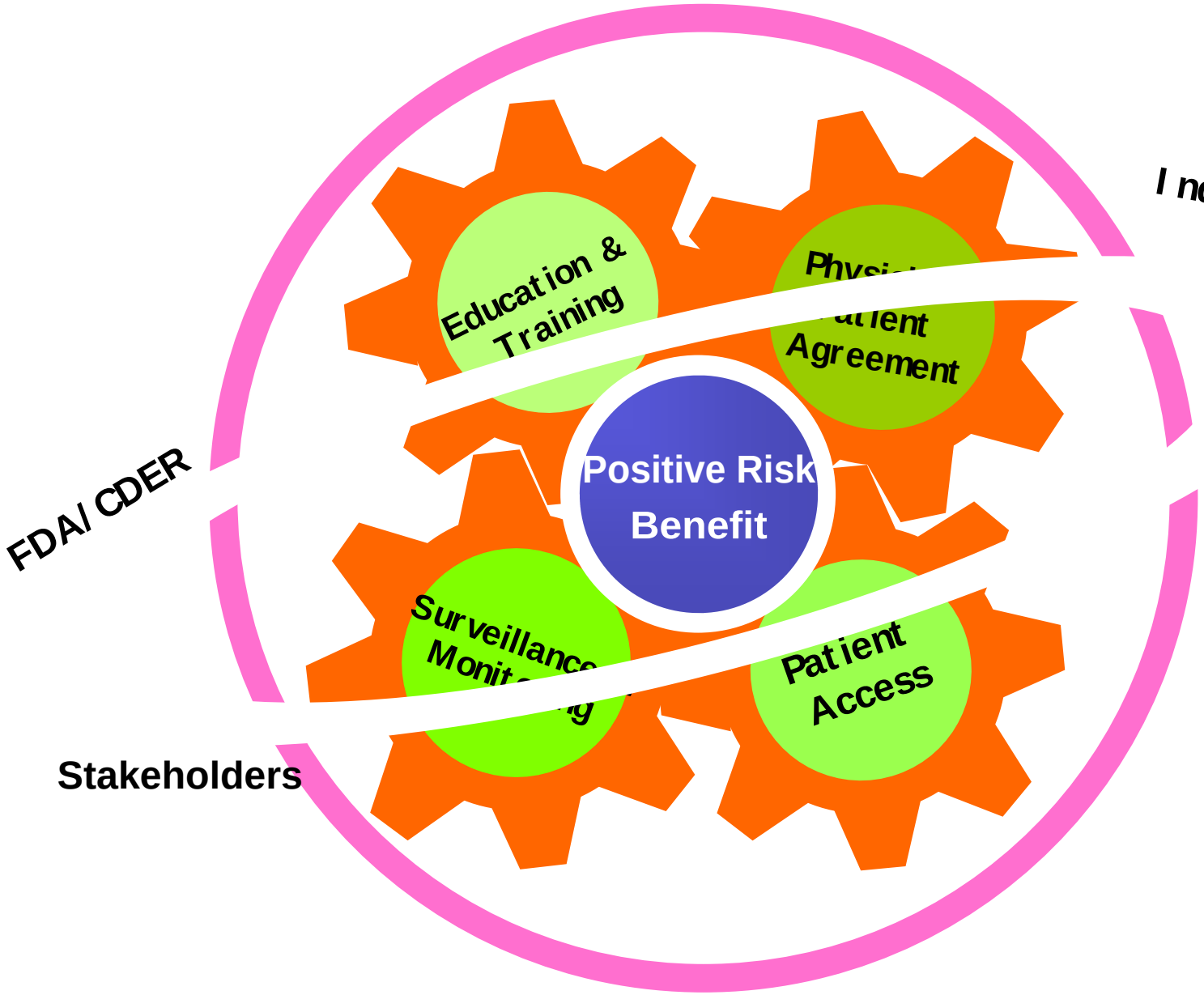
Onsolis – REMS

- Restricted distribution program
- Each patient, distributor, and pharmacy must enroll in the program
- Training & educational materials for prescribers and pharmacies
- Patient education & counseling
- Disposal directions of unneeded drug

Onsolis – REMS Goals

- Lessen the risk of overdose, abuse, misuse, addiction and serious complications due to medication errors:
- Proper patient selection, including avoiding use in opioid non-tolerant patients
- Reduce the risk of exposure in persons for whom it was not prescribed, including accidental exposure in children; and
- Train prescribers, pharmacists, and patients about proper dosing and administration

REMS Vision for Opioids



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- Expertise
- Technology
- Innovation
- Expanded Participation