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FDA's "Class-Wide" Risk Evaluation and Mitigation Strategies for Opiates: A Legal Perspective

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Topics of Discussion

- REMS Background
 - The Basics
 - Necessary Findings
 - Possible Elements
 - Procedures
 - Generic Drugs
- The “Class-Wide” Opiate REMS – Legal Issues
 - What Are the Drugs/What’s The Risk
 - Which Elements Are Proposed
 - Where Does It Stand
 - Legal Issues
 - Recent Approvability Decisions



REMS Background

REMS – The Basics

- FDAAA Title IX
 - Subtitle A – Postmarket Studies and Surveillance
 - Section 901
 - Postmarket studies and clinical trials regarding human drugs
 - Risk evaluation and mitigation strategies
 - Applies to NDAs, ANDAs, and BLAs
 - Effective March 25, 2008



REMS – The Basics

- New FDCA § 505(p)
 - Prohibits introduction of a new drug into interstate commerce if
 - a REMS is required and
 - the applicant fails to maintain compliance with the REMS
- New FDCA § 505-1
 - Statutory framework for integrating existing REMS tools into drug reviews and post-market pharmacovigilance



REMS – The Basics

- Initial Approval
 - FDA may request REMS as part of an NDA if necessary to ensure drug's benefits outweigh its risks
 - Considerations:
 - Size of population likely to use the drug
 - Seriousness of disease
 - Expected benefit with respect to disease
 - Duration of treatment
 - Seriousness of known/potential adverse events
 - Incidence of event in population likely to use drug
 - Whether the drug is a new molecular entity



REMS – The Basics

- Post-Approval
 - REMS may be required after initial approval if FDA
 - Becomes aware of new safety information, AND
 - Makes a determination that REMS is necessary to ensure that the benefits of the drug outweigh the risks
 - Proposed REMS must be submitted within 120 days after FDA notifies the NDA holder
 - FDA discretion to alter timeline



REMS – The Basics

- **Post-Approval REMS**
 - “New safety information” can be derived from
 - Clinical trial
 - Adverse event report
 - Postapproval study
 - Peer-reviewed biomedical literature
 - Postmarket risk identification and analysis system
 - Other scientific data deemed appropriate by FDA



REMS – Necessary Findings

- Post-Approval REMS
 - New safety information must be about:
 - A serious risk or an unexpected serious risk associated with use of the drug that FDA has become aware of since the drug was approved, since the REMS was required, or since the last assessment of the approved REMS for the drug
 - May be based on a new analysis of existing information
 - The effectiveness of the approved REMS obtained since the last assessment



REMS – Possible Elements

- Timetable for submission of assessment
 - At least at 18 months, 3 years, and 7 years
 - FDA may eliminate assessments after three years
- Additional elements as necessary
 - Medication Guide
 - Patient Package Insert
 - Communication plan to healthcare providers
 - Dear Doctor/Pharmacist Letters
 - Communication to professional societies
 - Professional education (speaker's bureau)



REMS – Possible Elements

- Additional elements as *necessary to assure safe use*
 - Distribution and/or use restrictions
 - Training or experience requirements for HCP
 - Special certification for drug prescribers
 - Special certification of pharmacies/drug dispensers
 - Limit dispensation to patients in certain health care settings
 - Documentation of safe use (laboratory test results) prior to dispensation
 - Specific patient monitoring
 - Patient registries



REMS – Possible Elements

- Conditions for ETASU
 - Known serious risks that would otherwise make the drug unavailable
 - Elements must be commensurate with specific risk
 - Elements must not be unduly burdensome on patient access
- To the extent practicable
 - Conform with elements used to assure safe use for other drugs with similar, serious risks and
 - Be compatible with established distribution, procurement, and dispensing systems for drugs



REMS – Possible Elements

- Additional elements as *necessary to assure safe use*
 - FDA must post for public review within 30 days of imposition
 - Include explanation of how the limitations will mitigate the safety risk
 - To the extent practicable
 - Conform with elements used to assure safe use for other drugs with similar, serious risks and
 - Be compatible with established distribution, procurement, and dispensing systems for drugs



REMS – Procedures

- Who is involved at FDA?
 - Section 505-1 specifically requires
 - The office responsible for reviewing the drug
 - OND
 - The office responsible for post-approval safety
 - ODS, OSE
 - Current experience adds
 - Office of Regulatory Policy
 - Office of the Chief Counsel



REMS – Generic Drugs

- Only two elements of the NDA REMS
 - Medication Guide and patient package insert (PPI)
 - Distribution and/or use restrictions
- Single shared system for distribution/use restrictions
 - FDA may waive this requirement
 - FDA may seek to negotiate license with NDA holder
- FDA will undertake any communication plan to HCPs



REMS – Generic Drugs

- Anti-blocking provision
 - No NDA holder shall use any element to assure safe use required by FDA to
 - Block or delay approval of an ANDA or 505(b)(2) NDA or
 - To prevent application of such element to a generic drug



REMS – Generic Drugs

- Thalomid (thalidomide)
 - Approved July 1998 with a Subpart H restricted distribution program
 - Product is deemed to have a REMS under FDAAA
 - Citizen petition requests that FDA not approve generics
 - Mere existence of multiple RiskMAPs creates increased risk of confusion and medical errors
 - Petition predates FDAAA



The “Class-Wide” Opiate REMS –
Legal Issues

What are the Drugs/What's The Risk?

- The Affected Drugs
 - Brand and generic drugs formulated with fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone
- What is the Risk
 - Use in non-opioid-tolerant individuals
 - Abuse (Misuse?)
 - Overdose (accidental and intentional)



Which Elements Are Proposed?

- MedGuide
- Elements to Assure Safe Use
 - Physician and Other HCP Certification
 - Prescriber is familiar with educational materials, drug risks and conditions for safe use
 - Will require physician-patient agreement
 - Will counsel patients
 - Physician Training
 - Proper patient selection
 - Appropriate dosing and administration
 - Identifying patients at risk of addiction
 - Risk of overdose/addiction from misuse of ER formulations



Which Elements Are Proposed?

- Elements to Assure Safe Use
 - Patient-Physician Agreements
 - Patient requires round the clock opiate for extended period to manage pain
 - Patient has been counseled about the risks and benefits
 - Patient has been given MedGuide
 - Patients being prescribed higher doses are opioid tolerant
 - Pharmacist Certification
 - Familiar with educational materials, drug risks and conditions for safe use
- Implementation System
 - Database of all enrolled entities
 - Plan to monitor and evaluate REMS implementation



Where Does It Stand?

- February 6
 - Notification of REMS decision to manufacturers
- March 3
 - Meeting with industry (closed door)
- May 27-28
 - Public stakeholder meeting
- Still to come
 - Other meetings (Advisory Committee)
 - Issue REMS letters/Federal Register notices



Legal Issue – Adequate Findings?

- Necessary Findings for Post-Approval REMS
 - FDA becomes aware of new safety information
 - A serious risk or an unexpected serious risk associated with use of the drug *that FDA has become aware of since the drug was approved*
- Enough Basis?
 - Is there really a serious risk that FDA became aware of after approval (or just a new source of information about a known risk)?
 - “Rates of misuse, abuse and accidental overdose have risen over the past decade”
 - Postmarketing reports of overdose, abuse and addiction “were not available at time of approval”
 - “Opioid abuse and misuse continues to grow”
 - Data shows increase between 2002 and 2007



Legal Issue – Adequate Findings?

- Necessary Findings for Post-Approval REMS
 - REMS is necessary to ensure that the benefits of the drug outweigh the risks
- Necessary Findings for ETASU
 - Known serious risks that would otherwise make the drug unavailable
- Enough Basis?
 - Would FDA withdraw approval of all these products if REMS not in place?
 - If not, then REMS are not “necessary”



Legal Issue – Adequate Findings?

- Other Conditions for ETASU
 - Elements must be commensurate with specific risk
 - Elements must not be unduly burdensome on patient access
- Are legitimate patients denied drug?
 - What evidence does FDA have that the REMS elements will be effective?
 - Physician certification will decrease number of prescribing physicians
 - Patients may be switched to less restricted (less safe or effective) therapies



Legal Issue – FDA Authority?

- Does FDA authority extend beyond the drug's label?
 - In order to be approved, drugs must be safe under the “conditions prescribed, recommended or suggested in the proposed labeling”
- FDCA 505-1 arguably expands that authority
 - FDA can consider the seriousness of known/potential AEs that may be related to the drug and the background incidence of such events in the population likely to use the drug
 - E.g., Testosterone REMS, fetal harm



Legal Issue – Equity

- Is the REMS really class-wide?
 - Affects fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone
 - No oral transmucosal fentanyl products
 - No hydrocodone, meperidine, codeine or buprenorphine products
 - No combination products
 - No meperidine or codeine products



Recent Approvability Decisions

- Onsolis
- Embeda
- Fentora (new indication)





QUESTIONS?

