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Risk Evaluation and Mitigation Strategies: FDA's New Authority

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Outline

- Past
 - Risk Management Plan (RMP)
 - Risk Minimization Action Plan (RiskMAP)
- Present
 - Risk Evaluation and Mitigation Strategies (REMS)
 - How FDA has implemented the REMS provisions
- Future
 - Opioid REMS
 - Challenges

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The Past



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FDA's concept of Risk Management

The overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit-risk balance.*

*Guidance for Industry Development and Use of Risk Minimization Action Plans (March, 2005)
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Risk Management

- Historically risk management included:
 - Prescription status
 - Labeling requirements
 - Postmarketing safety reporting requirements
- Risk management programs go beyond this

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FDA's Role in Risk Management Programs

- FDA has experience with risk management programs for about 20 years
- Generally thought of as restricted distribution programs
- In the past there was no standardization within FDA
- Only about a handful before 2000

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Early RMPs: Accutane Pregnancy Prevention Program

- Implemented following 1988 Dermatologic Advisory Committee meeting
- RMP elements included:
 - Informed Consent
 - Kit for prescribers
 - Accutane Survey and Prescriber Tracking Survey

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Early Restricted Distributions Programs

- **Clozaril: "No Blood, No Drug"**
 - Implemented at time of initial approval in 1989
 - RMP requirements:
 - Mandatory WBC monitoring
 - Patient registration in Clozaril National Registry
 - Enrollment of prescribers and pharmacies
- **Thalidomide: S.T.E.P.S. Program**
 - Approved in 1998 under subpart H regulations with restrictions
 - RMP requirements:
 - Enrollment of prescriber, pharmacy, and all patients
 - Pregnancy testing + use of reliable contraception
 - Telephone survey by prescribers and patients
 - Voluntary survey of subset of females of child bearing potential

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RiskMAPS

- FDA approved certain drugs and biologic products with Risk Minimization Action Plans (RiskMAPs)*
 - Those that required restricted distribution programs were sometimes approved under 21 CFR 314 Subpart H (e.g., thalidomide) or 21 CFR 601 Subpart E

•Guidance for Industry Development and Use of Risk Minimization Action Plans (March, 2005) 10

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Institute of Medicine Report (Sept 2006)



- *The Future of Drug Safety – Promoting and Protecting the Health of the Public*
- Recommendations included:
 - Labeling requirements and advertising limits
 - Clarification of FDA's authority and additional enforcement tools
 - Clarification of FDA's role in gathering and communicating information on risks and benefits of marketed drugs
 - Registration of clinical trials results
 - Increased role of FDA's drug safety staff
 - Increase in funding and staffing

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Food and Drug Administration Amendments Act (FDAAA)

- Enacted September 27, 2007
- Title IX, Subtitle A effective March 25, 2008
 - New authorities to require:
 - Postmarket studies and clinical trials
 - Safety labeling changes
 - Risk Evaluation and Mitigation Strategies (REMS)

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An Evolving Landscape

- Risk Management Program (RMP)
 - Original term
- Risk Minimization Action Plan (RiskMAP)
 - Guidance document: use started in 2005
- Risk Evaluation and Mitigation Strategies (REMS)
 - FDAAA: currently used

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The Present



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What is a REMS?

- A required risk management plan that utilizes tools beyond routine labeling to ensure that the benefits of a drug outweigh its risks.
- Applies to approved Rx drugs, including biologics and generics
- Does not apply to OTC products

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New REMS Provisions

- Preapproval:
 - If FDA determines that a REMS is necessary to ensure the benefits outweigh the risks
 - Approved at time of initial approval of drug
- Postapproval:
 - If FDA becomes aware of new safety information and determines that a REMS is necessary to ensure the benefits outweigh the risks
 - Sponsor must submit proposed REMS within 120 days, or within such other reasonable time as FDA requires to protect the public health

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Authorities 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

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REMS Considerations

- Certain factors must be considered:
 - Size of population likely to use drug
 - Seriousness of disease
 - Expected benefit of drug
 - Expected duration of treatment
 - Seriousness of known or potential adverse events
 - Whether the drug is a new molecular entity

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What's in a REMS for NDAs & BLAs?

- Every REMS must have a timetable for submission of assessment
- A REMS may contain:
 - Medication Guide (if meets existing regulatory requirements) or Patient Package Insert (*if insert may help mitigate serious risk of the drug*)
 - Communication plan if FDA determines plan may support implementation of an element of the REMS
 - Elements to assure safe use (previously known as distribution restrictions)

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Timetable for Submission of Assessments

- A timetable for when the sponsor will submit an assessment of the REMS – is it working?
- Minimum: Must assess by 18 months, 3 years, and in the 7th year after REMS approved
- FDA may specify different frequencies
- FDA can eliminate assessments after 3 years if it determines serious risks of the drug have been adequately identified and assessed and are being adequately managed

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Medication Guides and PPIs

- Medication Guide may be required
 - Distributed with every prescription dispensed
 - To provide information to patients when it is necessary to patients' safe and effective use of drug products
 - Help prevent a serious adverse event
 - Affect patient's decision to use, or continue to use the product
 - Directions for use are crucial to the drug's effectiveness
- Patient Package Insert (PPI)
 - Can be required as part of a REMS if FDA determines that such insert may help mitigate a serious risk of the drug.

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Communication Plans

- FDA “may require that the responsible person conduct a communication plan to health care providers” if “such plan may support implementation of an element of the strategy.”
- Communication plan may include:
 - letters to health care providers
 - disseminating information about the REMS to encourage implementation
 - disseminating information through professional societies about any serious risks of the drug and any protocol to assure safe use
- When a generic application is approved, FDA must implement the communication plan

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Elements to Assure Safe Use (ETASU)

- Required to assure the safe use of a drug –used to be called “restricted distribution”
 - Drug is associated with a serious adverse events and can be approved only if such elements are required as part of a REMS to mitigate a specific serious risk listed in the labeling, or would be withdrawn if elements are not part of REMS
 - Required only if we determine other elements are not sufficient to mitigate the risks
- All REMS with one or more ETASUs must include one or more goals to mitigate a specific risk listed in the labeling

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What are the ETASUs?

REMS may require or specify that:

- Health care providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug may be dispensed only in certain health care 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

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Elements to Assure Safe Use

- Must be commensurate with the specific serious risk listed in the labeling
- Can't be unduly burdensome on patient access to the drug
 - patients with serious or life-threatening diseases
 - patients who have difficulty accessing healthcare
- To the extent practicable, to minimize the burden on the healthcare delivery system, must conform with other elements for other drugs with similar serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

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A: Certification of Providers

- Health care providers who prescribe the drug have particular training or experience, or are specially certified
- Certifications may require that prescribers:
 - Are familiar with educational materials, risks of the drug, and conditions for safe use
 - Can diagnose and treat potential adverse reaction or are familiar with required monitoring

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B: Certification of Dispensers

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- Certifications may require that dispensers:
 - Are familiar with educational materials, risks of the drug, and conditions for safe use
 - Have special training on how to administer a product
 - Agree to fill a prescription only after receiving prior authorization

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C: Dispensed in Certain Settings

- The drug is dispensed to patients only in certain health care settings
 - Product can only be administered in hospitals or infusion centers

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D: Documentation of Safe-Use

- The drug be dispensed to patients with evidence or other documentation of safe-use conditions
- Evidence of safe use conditions may include
 - Laboratory tests
 - Documentation of consent or counseling by patient
 - Patient enrollment in a program that is designed to make sure patient is counseled about the risks of the drug, the importance of follow-up, monitoring if applicable, and reporting of adverse events
 - Patients receive the drug only after specified authorization is obtained (e.g., documented negative pregnancy test)

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E: Patient Monitoring

- Each patient using the drug is subject to certain monitoring
 - Might require periodic blood tests or other monitoring at specified time periods
 - Might require follow up questionnaire at specified time periods and after discontinuation of drug

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F: Registry

- Each patient using the drug be enrolled in a registry
 - Provides information on patients prescribed the drug and allows follow-up on adverse events and trends (e.g. pregnancy registry)

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FDA can require an applicant to have an implementation system

- If the REMS has any of these three ETASUs:
 - B. Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;
 - C. The drug is dispensed to patients only in certain health care settings, such as hospitals;
 - D. The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
- Take reasonable steps to monitor, evaluate, and work to improve implementation by healthcare providers and other participants

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REMS Assessment Plans

- Might include information about, for example:
 - Use data: what patients are getting the drug and under what conditions of use
 - Healthcare professionals' and patients' understanding regarding the safe use of the drug through surveys
 - Summary of adverse events associated with the drug that the REMS was designed to address
- Based on the information provided, will include an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

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REMS and Generic Drugs

- Generic drugs are only required to have Medication Guides or PPIs, and elements to assure safe use if the reference listed drug has a REMS with these elements
- If there was a communication plan for the innovator, FDA must carry out the plan when a generic is approved
- FDAAA states that generics must use a single shared system or obtain a waiver

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What about drugs that were approved before FDAAA?

- Certain approved products were deemed to have an approved REMS if they had elements to assure safe use
 - FR Notice (March 27, 2008) identified 16 products/28 applications
 - Products with restricted distribution systems
 - Proposed REMS were submitted and are currently under review
- Products with Medication Guides, PPIs, or Communication Plans before March 25, 2008 not converted to REMS – but those components continue

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Approved REMS

- Of over 260 CDER approvals of applications and efficacy supplements between March 25, 2008 and June 1, 2009:
- 51 approved REMS
 - 43 with Medication Guide only REMS
 - 8 with REMS that included more than a MG
 - Of those 8, 4 had elements to assure safe use
- 1 deemed REMS approved
- FDA website with approved REMS: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

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The Future

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Assess How Well It's Working

- We're collecting data on challenges associated with implementation of risk management plans many of which are applicable to REMS
 - Public meetings on risk management plans
 - Transcripts from the July 2007 RiskMAP public workshop:
 - patient advocacy panel
 - providers and payers panel
 - pharmacists and distributor panel
 - industry panel
 - "Therapeutic Risk Management Interventions: Feasibility and Effectiveness" (2004) by Andrews et al, *Journal of the American Pharmacists Association*

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Stakeholder Input

- PDUFA IV:
 - FDA will hold a public workshop to obtain input from industry and other stakeholders regarding prioritization of the RiskMAP, REMS, and communication tools to be evaluated
 - Conduct annual public discussion and review of effectiveness of one to two risk management program(s) with one major risk management tool
- FDAAA 505-1(f)(5): FDA and the Drug Safety and Risk Management Advisory Committee will:
 - Seek input from patients, physicians, pharmacists, and other health care providers on how elements to assure safe use can be standardized
 - To not be unduly burdensome on patient access to the drug
 - To the extent practicable, minimize burden on health care delivery system
 - At least annually evaluate elements to assure safe use for one or more drugs

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Opioid REMS

- FDA has announced that certain long-acting and extended-release opioid drugs must have REMS
- Unprecedented challenges to develop REMS
 - Opioids prescribed by over 100K different prescribers on a monthly basis
 - Over 3.7 million patients were prescribed opioids in year 2007
 - Almost every pharmacy dispenses them

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Opioid REMS (cont.)

- FDA has asked brand and generic sponsors to work together to develop a single shared system for opioid REMS
 - Different pieces may be provided by different parties (e.g., prescriber education, pharmacist education)
 - Will need centralized system or systems to ensure prescribers and pharmacists are certified and patients are counseled on risks and appropriate use of the drugs
- Opioid REMS may be a model for better ways to implement REMS

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Challenges

- How to facilitate the implementation of different programs with different requirements
- How to integrate REMS requirements with risk management plans developed by health plans and PBMs
- How to provide comprehensive information about REMS to pharmacists

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Challenges (cont.)

- How to include REMS in a pharmacy workload which relies on technology and automated systems
- How to allow dispensing in emergency situations
- How to maintain continuity of care with restricted distribution programs

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Conclusions

- We are preparing guidance for industry on REMS submissions
- We are working to ensure consistent application of the new REMS authorities
- We are using the authorities judiciously
- We will be evaluating the impact of our actions to determine whether they are having the beneficial effects we expect, whether there are any unintended adverse consequences, and whether improvements can be made in how we are implementing REMS
- We will continue to seek stakeholder input to improve REMS and encourage your participation

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Questions?

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