Risk Evaluation and Mitigation Strategies (REMS)

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Objectives

• Define REMS.
• Understand the evolution of REMS.
• Describe components of REMS.
• List the factors considered by the FDA when assessing the need for REMS.
• Describe an example of a REMS program.
• Identify problems with assessing the cost and outcomes of REMS.
• Identify opportunities for pharmacist leadership in REMS programs.
History of Risk Management

• Most basic tools: product labeling and drug approval\textsuperscript{1,2}

• 1976: 1\textsuperscript{st} mandatory PPI required for oral contraceptives\textsuperscript{1,2}

• 1999: Medication Guides introduced\textsuperscript{3}

• 2005: Risk Minimization Action Plans (RiskMAPs)
  – Used to meet product-specific risk-related goals/objectives to minimize risk while sustaining benefits\textsuperscript{1,2}
  – For products that pose a clinically important or unusual level of risk\textsuperscript{5}
  – Different goals for different products
  – Issues concerning implementation due to lack of enforcement authority
Risk Evaluation and Mitigation Strategies (REMS)

- Food and Drug Administration Amendments Act (FDAA) Title IX of 2007
  - authorized FDA to require and enforce (REMS) when necessary
- Based off of RiskMAPs, but is well defined, assessed over time, and legally enforceable
- Applies to prescription drugs and biologic products when necessary
- Primary Goal: keeping patients safe
- Ensures benefits outweigh risks
- Aids in management of known risk or potential serious ADEs associated with a particular medication

Center for Medication Safety Advancement
Components of REMS

- Patient Package Insert
- “Elements to Assure Safe Use” (ETASU)
- Communication Plan
- Medication Guide

Figure 1: David KD. Food and Drug Administration. REMS Evaluations: What Have We Learned? Available at http://www.fdanews.com/ext/files/Conference/RMDSS10presentations/Davis-REMS%20Evaluations.pdf.

Figure 1

- Sponsor must put in place a system to control prescribing or dispensing
- Levels of control differ from program-to-program
- Risk Information for prescribers or other HCPs
- Risk information directed to patients
- Most common form
Components of REMS (cont’d)\(^5\)

- **Implementation System**
  - Monitoring, evaluating, and working to improve implementation of ETASU by pharmacists, providers, and other persons affiliated with the healthcare system

- **Timetable for REMS Assessments (required)**
  - 18 months
  - 3 years
  - 7 years
Factors assessed by FDA when considering need for REMS\textsuperscript{5}

- Population size of users
- Seriousness of disease
- Benefit expected from drug
- Expected treatment duration
- Severity of known/potential adverse events (ADEs)
- Whether or not the drug is a new molecular entity
Outcomes: Accutane (isotretinoin)\textsuperscript{11}

- Challenging to Measure
- Evolution of iPLEDGE program
  - 1\textsuperscript{st} generation risk management approach
    - PPI and patient brochure
  - 2\textsuperscript{nd} generation risk management approach: Pregnancy Prevention Program (PPP)
    - Labeling changes, educational materials for counseling, 3 mandatory risk management procedures prior to prescribing
    - Still 2.8-3.4 exposed pregnancies per 1,000 patients
Outcomes: Accutane (isotretinoin)\textsuperscript{11}

- 3rd generation risk management approach: System to Manage Accutane Related Teratogenicity (SMART)
  - Improved patient education, required negative pregnancy test, qualification stickers
  - Pregnancy rate did not decline
- 4th generation risk management approach: iPLEDGE
  - Prescribers, pharmacies, wholesaler distributors, and patients must register in database
  - 0.012\% fetal exposures versus previous 0.28\% with PPP and SMART
Advantages of REMS

• Promote safe and appropriate use of drugs
• Provide opportunities for systematic data collection, reporting, and feedback on medication safety
• Allow drugs to be approved that would not otherwise have been approved because of risks
• Allow drugs that might have been withdrawn from the market because of risks to remain on the market
• Provide opportunities for expanded clinical and leadership roles and collaboration among pharmacists, physicians, and other healthcare practitioners
Disadvantages of REMS

- Lack of standardization
- Potential for Confusion among healthcare practitioners
- Time-consuming, labor-intensive nature
- Lack of reimbursement for extra work involved
- Insufficient healthcare practitioner input in FDA in premarketing development of REMS
- Potential for disruption in continuity of patient care
Challenges with REMS

• Implementation of REMS requirements
  – Study by Childs et al. implemented quality-improvement initiatives to increase compliance with REMS requirements\(^{14}\) “staff education, incorporation of REMS requirements into existing policy, development of an electronic resource, and creation of a separate storage section for drugs subject to REMS”

• No standardization
Costs of REMS

• Challenging to quantify costs\textsuperscript{15}
• Hard vs. soft costs
• Costs to manufacturer\textsuperscript{15}
  – $5,000-$500,000
  – 20-120 days of development time
  – Drug approval rates, timeline, setup and monthly maintenance\textsuperscript{15,16}
  – Sales impact
• Costs to distributors\textsuperscript{15}
  – $5,000- $1,000,000
Costs of REMS

• Cost to providers\textsuperscript{16}
  – Offices/hospitals
  – Policies, procedures, personnel, time, information technology
  – Registration/certification
  – Record keeping
  – Reporting to manufacturer

• Cost to patients
  – Accessability
  – Time
  – Inconvenience
Opportunities for pharmacist leadership

• Actively participate in development & implementation of strategies
• Managing clinical & distributive therapeutic areas requiring REMS
• Pharmacists are uniquely qualified
• Comprehension of clinical care, systems of drug distribution, attention to detail
• P&T Committees
• Continuing-education seminars
Opportunities for pharmacist leadership

- Publications
- Inservice education
- Professional meeting presentations
- Provider, resident, and student education
- Insight on program design and advocacy to improve program design
- Technician opportunities as well
- Record keeping
References


References


