



An Overview of RiskMAPs

**Office of Surveillance and
Epidemiology**

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Outline

- Background of risk management at FDA
- Risk Minimization Action Plan (RiskMAP)
- FDA experience with RiskMAPs
- RiskMAP evaluation



Background of Risk Management at FDA



Risk Management at FDA

- FDA has been involved in the management of drug risk for years
- Early risk management programs that preceded “RiskMAPs”:
 - Clozapine – “no blood, no drug” program
 - Implemented in 1990
 - Developed to prevent agranulocytosis
 - Thalidomide – System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) Program
 - Implemented in 1998
 - Developed to prevent fetal exposure



FDA Risk Management Documents

- Managing the Risks from Medical Product Use
 - Report to the FDA Commissioner from the Task Force on Risk Management
 - Task force asked to examine the current system to manage risks associated with using medical products
 - Focus on FDA's role in the system
 - Published May 1999



FDA Risk Management Documents

- FDA Risk Management Guidance Documents

- Developed in response to Prescription Drug User Fee Act III (PDUFA III) that authorized June 2002.
 - One of goals was to produce guidance for industry on risk management activities for drug and biological products
 - Finalized March 2005



Risk Management Guidance Documents

- Premarketing Risk Assessment
 - <http://www.fda.gov/cder/guidance/6357fnl.pdf>
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
 - <http://www.fda.gov/cder/guidance/6359OCC.pdf>
- Development and Use of Risk Minimization Action Plans (RiskMAP)
 - <http://www.fda.gov/cder/guidance/6358fnl.pdf>



Risk Minimization Action Plan (RiskMAP)



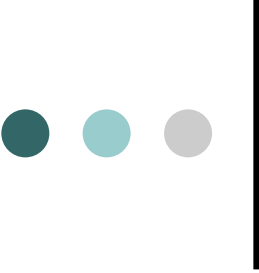
Risk Management Definition

- An iterative process of
 - assessing a product's benefit-risk balance,
 - developing and implementing tools to minimize its risks while preserving its benefits,
 - evaluating tool effectiveness and reassessing the benefit-risk balance, and
 - making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance



Risk Minimization Action Plan (RiskMAP) Definition

- A RiskMAP is a strategic safety program
 - Designed to meet specific *goals* and *objectives* in minimizing product risks while preserving benefits
 - Uses one or more tools to meet goal(s)
 - Goes beyond FDA-approved labeling



RiskMAP Goals and Objectives

- Goals: targeted specific health outcome related to known safety risk
 - Should be stated in absolute terms
 - Example: Fetal Exposure to Drug X should not occur
- Objectives: Intermediate step to achieving the goal(s)
 - Should be measurable
 - Example: All females of childbearing potential will have a pregnancy test before taking Drug X



Tools

- Tool – a process or system intended to enhance safe product use by reducing risk
- Tool Categories:
 - Education and outreach
 - Reminder/prompting systems
 - Restricted Distribution Systems - referred to Performance-linked Access Systems (PLAS) in Guidance



Tool Categories: Education and Outreach

○ Purpose

- Communicates specific risks of treatment that are of concern
- Increases knowledge of key stakeholders (HCPs and/or patients) who have capacity to prevent or mitigate product risks
- Provides description of the RiskMAP
- Can be used to:
 - Encourage participation in plan assessment activities such as surveys
 - Encourage reporting of adverse events



Tool Categories: Education and Outreach

- Examples include:
 - Medication guides,
 - RiskMAP program guides,
 - Videos/DVDs,
 - DHCP letters, and
 - Continuing education units



Tool Categories: Reminder/Prompting Systems

- Purpose

- Prompting, reminding, double-checking, or otherwise assisting healthcare providers in following appropriate prescribing, and/or dispensing practices
- Assisting patients or caregivers in their receipt and use of the drug in ways to minimize risk



Tool Categories: Reminder/Prompting Systems

- Examples include:
 - MD-patient agreements
 - Patient acknowledges that s/he is aware of drug risk and what behaviors will minimize risk
 - Attestation or acknowledgment
 - Physician acknowledges that s/he will obtain necessary testing prior to prescribing drug
 - Pharmacy may also be asked to attest to complete certain procedures
 - Pharmacy checking mechanisms (stickers)
 - Pharmacist checks for sticker to verify that mandatory risk minimization procedures are completed



Tool Categories: Restricted Distribution or PLAS

- Purpose

- Limits drug access to targeted patient population
- Useful for drugs with unique benefit but also unusual risk

- Examples include

- Mandatory registries or enrollment of patients, prescribers, and/or pharmacists
- Mandatory patient monitoring
- Prescribing, distribution, and dispensing restrictions



Guidance Recommends the Following During RiskMAP Development

- Maintaining product access
 - Try to avoid unintended consequences
- Select tools with evidence of effectiveness (if possible)
- Get stakeholder input
- Consider current technology and settings that drug will be used



FDA Experience with RiskMAPs



Risk Management Activity at FDA

- 130 Risk Management Plans submitted for review between Oct 2002 (start of Risk Management Program) and Dec 2006
 - Some submissions considered routine risk management
 - Some submissions revised after Agency comments and re-submitted



Risk Management at FDA

- As of February 2007, there were 30 drugs with some type of RiskMAP
 - Most involve targeted education and outreach
 - 9 plans developed post-marketing
 - 10 plans include performance-linked access



Tools

- Education tools
 - Common in all RiskMAPs
 - Often the primary tool
 - Targeted to relevant stakeholders
 - Medication guides for patients
- Other tools will be the focus of this workshop
 - Reminder systems and performance-linked access systems



Experience: Reminder Tools

- Limited supply of drug
 - Isotretinoin – 30 days
 - Thalidomide, Lenalidomide – 28 days
 - Clozapine – 7 days, then 14 days, then 30 days
 - Lindane – maximum of 1 to 2 ounces
 - Sodium oxybate – 30 day supply initially

cbk2

does guidance go into the purpose of limiting amount dispensed? if so, could add

Claudia B. Karwoski, 6/11/2007



Experience: Reminder Tools

- Limits on refills – No refills
 - Isotretinoin
 - Lenalidomide
 - Thalidomide
 - Opioids (under DEA regulations)



Experience: Reminder Tools

- Pt-MD agreements/ informed consent:
 - Alosetron
 - Isotretinoin
 - Lenalidomide
 - Mifepristone
 - Nataluzimab
 - Thalidomide



Experience: Reminder Tools

- Physician attestation or acknowledgment
 - Alosetron
 - Isotretinoin
 - Natalizumab (also has patient acknowledgement)
- Stickers
 - Alosetron



Experience: PLAS

Registration/Enrollment of Prescribers

○ Drugs that require:

- Alosetron
- Bosentan
- Clozapine
- Dofetilide
- Isotretinoin
- Lenalidomide
- Mifepristone
- Natalizumab
- Sodium oxybate
- Thalidomide



Experience: PLAS Registration/Enrollment of Patients

○ Drugs that require:

- Bosentan
- Clozapine
- Isotretinoin
- Lenalidomide
- Nataluzimab
- Sodium oxybate
- Thalidomide



Experience: PLAS

Registration/Enrollment of Pharmacy

- Requires registration of pharmacy to dispense or treatment site to administer
 - Clozapine
 - Dofetilide
 - Isotretinoin
 - Natalizumab
 - Thalidomide



Experience: PLAS Special Distribution Procedures

- Dispensing by specialty distributors or central pharmacies
 - Lenalidomide
 - Bosentan
 - Natalizumab
 - Sodium oxybate



Experience: PLAS

Administration in Special Settings

- Product administration in medical setting
 - Mifepristone – administered in medical setting (doctor's office)
 - Dofetilide – requires inpatient hospitalization for 3 days when initiating therapy
 - Natalizumab – an IV biologic that requires administration by authorized infusion sites



Experience: PLAS Mandatory Tests

- Requires documented lab test prior to dispensing
 - Clozapine – WBC
 - Every 7 days for first 6 months; every 2 weeks until 1 year and then every 30 days
 - Isotretinoin, lenalidomide, thalidomide – negative pregnancy test
 - Pregnancy testing part of prescribing process



Restricted Distribution/PLAS

Example: Thalidomide (Thalomid)

- Indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and recently approved for treatment of multiple myeloma
- Safety Issue: Teratogenicity
- Approved with RiskMAP: System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)
 - Goal: to ensure that fetal exposure to thalidomide does not occur.



The S.T.E.P.S. Process

- All prescribers, patients, and pharmacies must register in S.T.E.P.S.
- Patients are counseled regarding the need to use appropriate contraception and the side effects associated with therapy
 - Pregnancy test must be performed within 24 hours of beginning therapy; conducted every week for 4 weeks and then every 4 weeks



Restricted Distribution/PLAs

Example: Thalidomide (Thalomid)

- Prescription process:
 - The prescriber completes a brief telephone survey and provides information to system
 - The patient must sign registration/informed consent
 - The patient must complete pregnancy tests
 - The patient completes a brief telephone survey and takes the prescription to the pharmacy

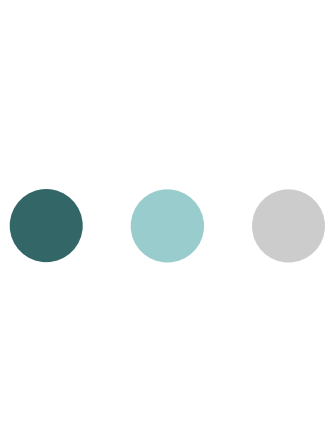


Restricted Distribution/PLAs

Example: Thalidomide (Thalomid)

- Prescription process (cont.):

- Registered pharmacy calls Customer Care Center and provides authorization number from the patient's prescription.
- If all requirements fulfilled, the pharmacy will receive a validation number that is recorded on the prescription.
- The pharmacy can then dispense up to a 28-day supply.



RiskMAP Evaluation



Why and When to Evaluate

- Intended to ensure that resources expended on risk minimization are achieving the desired goals
- Sponsors should:
 - Consider pre-testing in Phase III protocols
 - Develop evaluation plan for RiskMAPs
 - Timeline for evaluation should be submitted with plan
 - Components of evaluation plan should be discussed with Agency



What to Evaluate

- Evaluation of the performance of the overall RiskMAP in achieving its goals
 - Health outcomes or surrogates of health outcomes
 - Numbers or rates of an outcome or event
 - PLAS have denominator data for analysis
- Evaluation of the performance of the overall RiskMAP in achieving its objectives
 - Compliance with important RiskMAP processes and procedures
 - Assessment of comprehension, knowledge or desired behavior



Evaluation Tools

- Observational data
 - Drug use: patterns of prescribing and use
 - Population databases: assess outcomes and infer physician, patient behaviors
 - Assess laboratory monitoring, co-prescribing
 - Sponsor databases: monitor outcomes and process measures
- Conduct surveys
 - Assess physician/healthcare providers and/or patient
 - Knowledge
 - Compliance with RiskMAP process



How Information is Used

- Identify need for modification to RiskMAPs if goals not being met
 - Improve effectiveness, consistency
- Allows sharing of “lessons learned”
 - Public meetings (e.g. Advisory Cmtes) and
 - Web site for information sharing
 - Planning stages



What We Know About RiskMAPs

- Some evidence that RiskMAPs have been effective
 - Clozapine
 - Thalidomide
- Most programs still require evaluation
 - Use often too small to determine whether tools are effective in minimizing risk



What We Don't Know about RiskMAPs

- Don't know how many patients who could benefit don't have access to product
- Don't know how many prescribers decide to use other products with a similar indication because those drugs do not have RiskMAPs
- Don't know how many patients are going outside of RiskMAP to obtain product



Conclusions

- Risk management plans have been developed to minimize important drug risks.
- The number of plans has increased, but remains relatively small.
- A variety of tools have been used as part of approved plans.
- The evaluation of ongoing RiskMAPs is important to determine if proposed goals are being met and if modifications are needed.