An Overview of RiskMAPs

Office of Surveillance and Epidemiology

June 25, 2007

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 Pharmacoepidemiogic 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

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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.