Considerations for the Use of Risk Minimization Action Plans

FDA Draft Guidance and Experience

Anne Trontell, M.D., M.P.H.
CDER Office of Drug Safety

February 15, 2005

Outline

- Definitions of risk management and risk minimization
- Risk Minimization Action Plans
  - When are they needed
  - Design considerations and evaluation
- Experience

FDA Definition of Overall Process of 'Risk Management'

- An iterative process
  - Assessing benefit-risk balance
  - Use of tools to minimize risk and preserve benefits
  - Evaluation of tools, risks, and benefits
  - Reassessment of benefit-risk balance

FDA Definition of Overall Process of 'Risk Management

- An iterative process
  - Assessing benefit-risk balance
  - Use of tools to minimize risk and preserve benefits
  - Evaluation of tools, risks, and benefits
  - Reassessment of benefit-risk balance

Risk Management

II

Risk assessment

+

risk minimization efforts

Risk Assessment and Risk Minimization

Highly inter-related

- Occur both pre- and post-marketing
- Best if both are evidence-based

Risk minimization efforts are based upon good risk assessment

FDA Risk Management Guidances (Drafts)

- Development and Use of Risk Minimization Action Plans
- Premarketing Risk Assessment
- Good Pharmacovigilance and Pharmacoepidemiologic Assessment

FDA Risk Management Guidances (Drafts)

- **Development and Use of Risk Minimization Action Plans**
- Premarketing Risk Assessment
- Good Pharmacovigilance and Pharmacoepidemiologic Assessment

Risk Minimization Action Plans

- Term used in draft FDA guidance to distinguish risk minimization interventions from overall process of risk management
- **Risk M**inimization **A**ction **P**lan → RiskMAP

When is a RiskMAP Appropriate?

- It depends

Considerations:

- Nature and rate of known risks vs benefits
- What are risks and are they preventable?
  - Best if risks can be minimized or avoided by one or more preventive measures
- Probability of benefit

When is a RiskMAP Appropriate?

- No ready formula for comparing risks and benefits- decisions thus made on a case-by-case basis
- Employ RiskMAPs judiciously
  - Expect only a limited number of products to need RiskMAPs
  - For most products, risk minimization is accomplished via package insert (product labeling)

The Package Insert

- FDA-approved professional product labeling (package insert or PI)
  - the cornerstone of routine risk communication and risk minimization/management efforts
  - updated to reflect new benefits or risk concerns
  - ongoing efforts to make clear, concise and focused
- Not a RiskMAP in and of itself

Risk Minimization Action Plan (RiskMAP) Definition

- A strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits
- Uses one or more *tools* to accomplish these ends

RiskMAP Definitions

- Goal – End result, expressed in terms of one or more health outcomes to be achieved (or avoided)
- Objective – Intermediate step to achieving the goal(s)
- Tool – System or process other than product labeling

Definitions Applied to a Fictional Example

- Goal: A dangerous drug-drug interaction should not occur
- Possible Objectives:
  - Physicians won't co-prescribe 2 drugs
  - Pharmacists won't co-dispense
  - Patients won't take 1 drug with the other
- Tools: Education, pharmacy alert screens, or restrictions on physicians or others

Selecting RiskMAP Tools

Risk Minimization Tools

- Specialized communication of information to minimize risks
  - Do X
  - Don't do Y
- Alter typical methods of prescribing, dispensing, using product via
  - reminders (voluntary)
  - restrictions (mandatory)

Categories of RiskMAP Tools

- Targeted Education & Outreach
- Reminder Systems
- Performance-Linked Access Systems

Categories of RiskMAP Tools

- Targeted Education & Outreach
  - *–to inform*
- Reminder Systems
  - *–to nag or nudge*
- Performance-Linked Access Systems
  - *–to impose limits*

Targeted Education and Outreach

- Consider when risks cannot be minimized with routine measures alone (such as the PI)
- To increase knowledge of key stakeholders who have capacity to prevent or mitigate product risks

Education and Outreach

- Health care practitioner (HCP) letters
- Professional or public notifications
- Training programs for HCP or patients
- Continuing education for HCP
- Focused or limited product promotion
- Patient labeling
  - Medication Guides (MG)
  - Patient Package Inserts (PPI)

Medication Guides

- FDA approved patient labeling
- Regulated since 1999 (21 CFR Part 208)
- Required dispensing with each prescription
- Primarily for outpatient Rx products with serious & significant public health concerns

Medication Guides

- Three triggering criteria

  At least one criterion must be met

  – pt labeling could help prevent serious AEs
  – serious risks: could affect pt decision to use
  – pt adherence to directions crucial to effectiveness
- CFR 208.20 specifies format and content

Patient Package Insert (PPI)

- FDA approved patient labeling
- Not covered by regulation and not required to be dispensed with each prescription
  - Exception: Oral Contraceptives and Estrogens (21 CFR 310.501, 310.515)

Patient Package Insert (PPI)

- FDA recommends Medication Guide format & content to promote consistency and patient recognition
- Unit-of-use packaging with PPIs can function similarly to Medication Guide

Reminder Systems

- Use with targeted education
  - when education alone is insufficient to minimize risk(s)
- Prompt, remind, double-check or otherwise guide HCP or patients
  - prescribing, dispensing, receiving
- Alternatively stated, make it difficult to forget important safety processes

Reminder Systems

- Patient agreement/acknowledgement
- Practitioner attestation or certification programs
- Special conditions of dispensing
  - special packaging that limits amount or misuse
  - limited supply / no refills
  - system of records that remind/attest appropriate safety measures are done (e.g. stickers)

Performance-Linked Access Systems

- Use when targeted education and reminder systems are insufficient to minimize risk(s)
- For products with
  - significant/unique benefits but
  - unusual risks, fatal or irreversible
- Links drug product access to compliance with plan conditions
  - e.g. documentation of safe use conditions (such as lab tests)

Performance-Linked Access Systems

- "Involuntary" in the sense that access occurs only if compliant with procedures
- Examples
  - Clozapine
  - Thalidomide
  - Dofetilide

Selecting and Developing Tools
Consider:

- Seek to maintain appropriate product access
- Identify key stakeholder groups who have capacity to minimize risks
  - healthcare providers, patients, insurers
  - seek input on feasibility of tool(s)
  - minimize stakeholder burdens

Selecting and Developing Tools

Consider:

- Current technology
- Likely settings for product use
  - outpatient and inpatient
  - urban and rural
- Current evidence of effectiveness
  - in other RiskMAPs
  - in related area
- Seek to avoid unintended consequences

Evaluation

Collection of information on RiskMAP and tool performance is essential

- To achieve health outcomes/goals
  - effectiveness & value-added of tools
  - ensure energy/resources being expended actually achieve desired goals
  - stakeholder acceptability
  - compliance with procedures
- To identify areas for improvement

Experience/Lessons Learned

Examples of Products Using RiskMAP Tool Categories

- Targeted education and outreach
  - products with Medication guides, CME
- Reminder systems
  - alosetron, isotretinoin, lindane, abarelix
- PLAS
  - bosentan*, clozapine*, dofetilide*, mifepristone, thalidomide*, xyrem

* lab testing required

Targeted Education and Outreach Tools Advantages/Disadvantages

Advantages

- Acceptable to most
- Feasible
- No effect on access

Disadvantages

- General effectiveness often unstudied or limited
- Poorly effective in pregnancy prevention for isotretinoin (APCC), troglitazone LFT monitoring

Reminder Systems Advantages/Disadvantages

Advantages

- Physician, pharmacist, patient autonomy
- Ongoing education, reminders re risks and safe use
- Less intrusive than limited distribution

Disadvantages

- Time and $ costs
- Evaluations limited to sticker programs
- SMART showed high process compliance, limited outcome effectiveness; Lotronex system the reverse!

Performance-Linked Access Systems Advantages/Disadvantages

Advantages

- Limits access to those adhering to critical risk minimization tools
- Mandatory participation → registration, better data for evaluation
- System burdens alone likely to limit exposure to risk

Disadvantages

- Time and $ burdens
- Limits access to drug benefits
- May prompt illicit access without any safety measures
- Limited experience in large numbers of users

Summary: RiskMAPs

- Apply to a small number of products
  - PI still cornerstone of RM
- Have clear goals and objectives
- Use tools that
  - are evidence-based
  - allow product access that is appropriate
  - consider stakeholder input, technology, use settings, other factors
- Are evaluable and monitored

Web References

- Premarketing guidance

  http://www.fda.gov/cder/guidance/5767dft.pdf
- Pharmacovigilance guidance

  http://www.fda.gov/cder/guidance/5767dft.pdf
- RiskMAP guidance

  http://www.fda.gov/cder/guidance/5766dft.pdf